Chemoenzymatic Total Syntheses of the Enantiomers of the Protoilludanes 8-Deoxydihydrotsugicoline and Radudiol

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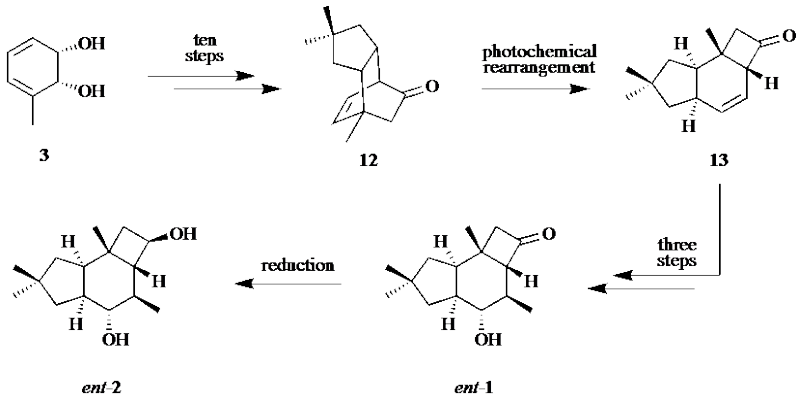


ABSTRACT: Chemoenzymatic and stereoselective total syntheses of the non-natural enantiomeric forms, *ent*-**1** and *ent*-**2** respectively, of the recently isolated protoilludane natural products 8-deoxydihydrotsugicoline (**1**) and radudiol (**2**) are reported. The key steps involve the Diels-Alder cycloaddition of cyclopent-2-en-1-one to the acetonide derived from enantiomerically pure and enzymatically-derived *cis*-1,2-dihydrocatechol **3**, elaboration of the resulting adduct to the tricyclic ketone **12** and a photochemically-promoted rearrangement of this last compound to the octahydro-1*H*-cyclobuta[*e*]-indenone **13**.

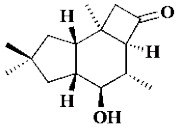
INTRODUCTION

Protoilludane-type sesquiterpenoids embody the distinctive perhydro-1*H*-cyclobuta[*e*]-indene or 5/6/4 tricarbocyclic framework and are produced by a range of higher order fungi *via* a humulene cyclization pathway.[1,2] New members of the class continue to be isolated at regular intervals[3] and various interesting biological activities have been attributed to a number of them. These activities include antibacterial, antifungal, cytotoxic and plant-growth regulating effects.[1,3,4] On this basis and because of their challenging structural features they have been the focus of significant and ongoing synthetic efforts.[1,5] Recently, we disclosed a chemoenzymatic synthesis of the melleolide or protoilludane aryl ester (+)-armillarivin.[5b] The first of two key chemical steps involved the high-pressure (19 kbar) promoted and facially selective Diels-Alder cycloaddition of an enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol with cyclopentenone. The second was a photochemically promoted 1,3-acyl migration (Givens rearrangement)[6] of a derivative of the cycloadduct that afforded the full 5/6/4-tricyclic framework of the target natural product.

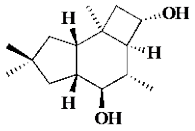
Herein we describe total syntheses of the enantiomers, *ent*-**1** and *ent*-**2** respectively, of 8-deoxydihydrotsugicoline (**1**)[3b] and radudiol (**2**),[3a,d] protoilludanes recently isolated from, *inter alia*, *Granulobasidium vellereum* (Ellis & Cragin) Jülich, a saprotrophic and rare wood-decay basidiomycete fungus encountered in deciduous forests throughout East Asia, North America and Europe (Figure 1). The structures of compound **1** and **2** were assigned using NMR, MS, CD and polarimetry techniques. The synthetic chemistry studies reported here, which are the first involving the title compounds, serve to confirm the structures of these natural products as well as demonstrate, when considered in

conjunction with our earlier work,[5d] that either enantiomeric form of the perhydro-1*H*-cyclobuta[*e*]indene framework can be obtained from the *cis*-1,2-dihydrocatechol **3** by controlling the facial selectivity of the Diels-Alder reaction of this diene and its derivatives with cyclopent-2-en-1-one.

Figure 1: *Structures of Protoilludanes **1** and **2**, their Enantiomers and the Metabolite **3** Used as the Starting Material in the Present Study*



1



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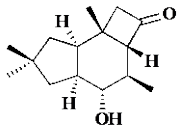
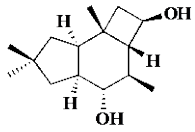
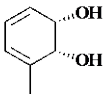


***ent*-1**



***ent*-2**

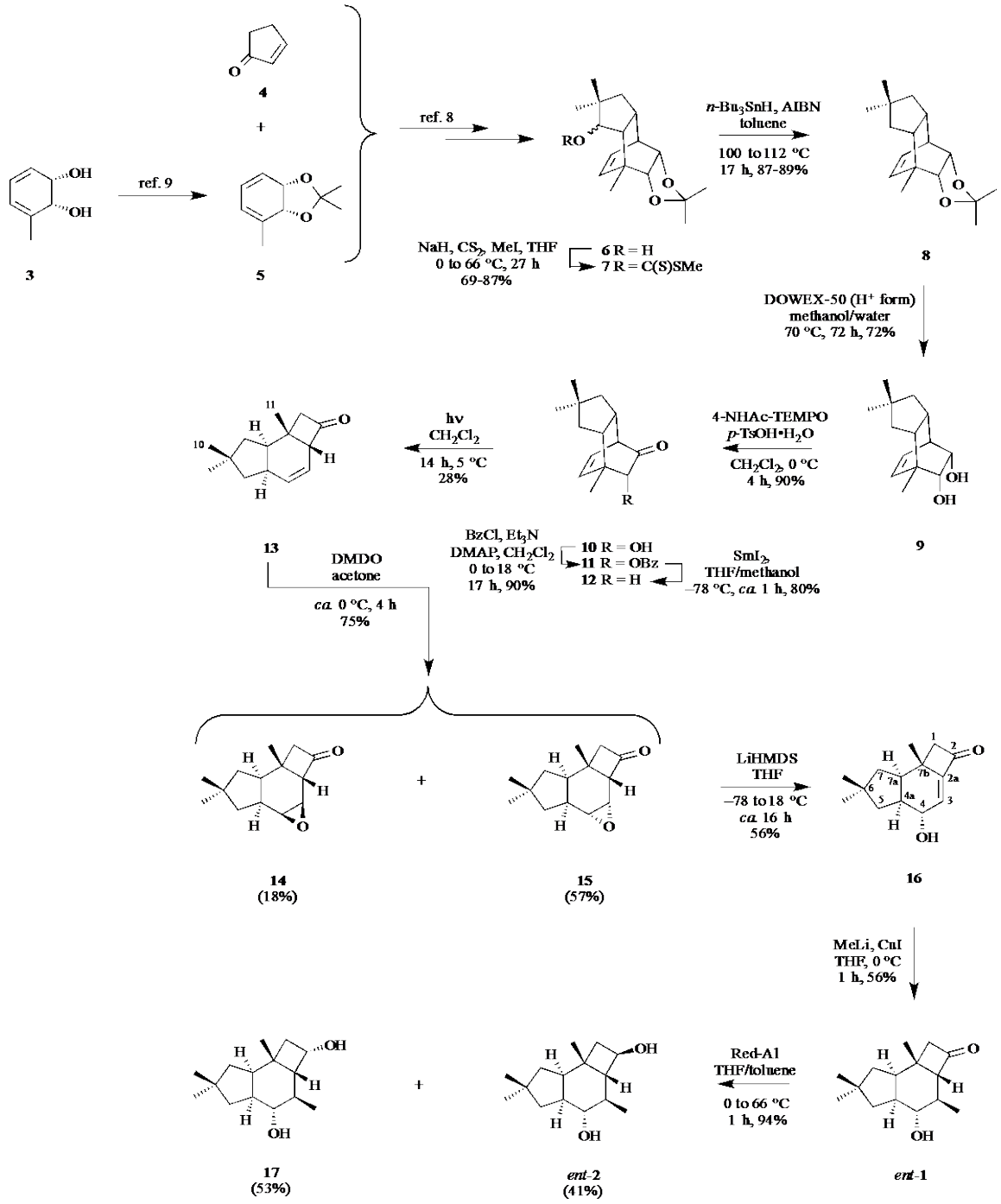


3

RESULTS AND DISCUSSION

The reaction sequence leading from metabolite **3**[7] to compounds *ent*-**1** and *ent*-**2** is shown in Scheme 1 and started with the previously reported[8] microwave-promoted Diels-Alder cycloaddition of 2-cyclopenten-1-one (**4**) with the acetonide, **5**,[9] derived from *cis*-1,2-dihydrocatechol **3**. The adduct (73%) thus obtained was *gem*-dimethylated by the means described in an earlier report from our group[8] and the product thus obtained (56%) reduced with $LiAlH_4$ to afford a *ca*. 3:2 mixture of the chromatographically separable and epimeric alcohols **6**[8] (97%). Each of these was converted into the corresponding methyl xanthate **7** (69-87%) under standard conditions and a single-crystal X-ray analysis conducted on the β-epimer served to confirm its structure (see Experimental Section and SI for details). Barton-McCombie deoxygenation[10] of these esters using *n*-Bu_3SnH in the presence of AIBN afforded the anticipated product **8** (87-89%) that upon treatment with acidified DOWEX-50 resin in aqueous methanol afforded the diol **9** (72%). Selective mono-oxidation of this last compound to acyloin **10** (90%) could be achieved using the sterically demanding oxoammonium salt derived from the *p*-toluenesulfonic acid-promoted disproportionation of 4-acetamido-TEMPO.[11] Compound **10** was converted into the corresponding benzoate **11** (90%) and samarium diiodide-promoted deoxygenation of the latter afforded the ketone **12** in 80% yield.

Scheme 1


3
ref. 9
4
+
5
ref. 8
RO
NaH, CS2, MeI, THF
0 to 66 °C, 27 h
69-87%
6 R = H
7 R = C(S)SMe
n-Bu3SnH, AIBN
toluene
100 to 112 °C
17 h, 87-89%
8
DOWEX-50 (H+ form)
methanol/water
70 °C, 72 h, 72%
9
4-NHAc-TEMPO
p-TsOH•H2O
CH2Cl2, 0 °C
4 h, 90%
R
hν
CH2Cl2
14 h, 5 °C
28%
13
BzCl, Et3N
DMAP, CH2Cl2
0 to 18 °C
17 h, 90%
10 R = OH
11 R = OBz
12 R = H
SmI2
THF/methanol
–78 °C, ca. 1 h, 80%
DMDO
acetone
ca. 0 °C, 4 h
75%
14
(18%)
15
(57%)
LiHMDS
THF
–78 to 18 °C
ca. 16 h
56%
16
MeLi, CuI
THF, 0 °C
1 h, 56%
17
(53%)
ent-2
(41%)
Red-Al
THF/toluene
0 to 66 °C
1 h, 94%
ent-1

In the second pivotal step of the reaction sequence a dichloromethane solution of the cyclopentannulated bicyclo[2.2.2]oct-5-en-2-one **12** was subjected to direct irradiation using a medium-pressure mercury vapor lamp and thus effecting the anticipated 1,3-acyl-migration reaction to produce the cyclobutanone **13** (54% at 51% conversion) that embodies the non-natural enantiomeric form of the protoilludane framework.[12] All of the spectroscopic data acquired on compound **13** were in complete accord with the assigned structure. Most notably, the infrared spectrum displayed a carbonyl group absorption band at 1781 cm^{-1} while the corresponding ^{13}C NMR spectrum showed the expected fourteen resonances including one at δ_C 206.4 that is attributed to the carbon of the same moiety. The two lowest field signals appearing at δ_H 5.64 and 5.50 in the ^1H NMR spectrum were mutually coupled (J = 10 Hz) one-proton multiplets that are assigned to the olefinic protons of the β,γ-unsaturated enone moiety of photoproduct **13**.

The elaboration of compound **13** to the target *ent*-**1** proved to be a straightforward matter that involved, as the first of three steps, treating the former compound with dimethyldioxirane (DMDO)[13] and so producing a *ca*. 3:1 mixture of the diastereomerically related and chromatographically separable oxiranes **14** (18%) and **15** (57%). Various considerations led to the assigned stereochemistries of these products. First of all, an inspection of a molecular model of the precursor **13** suggested that the β-face of the olefinic residue is the more congested one by virtue of the impinging C10 and C11 methyl groups. Furthermore, the ^1H NMR spectrum of the minor product **14** displayed, as expected, a greater spread of the chemical shifts of the three methyl group singlets (δ_H 1.16, 1.09 and 0.99) than observed in the corresponding spectrum of

congener **15** (δ_H 1.09, 0.97 and 0.96) wherein the epoxide oxygen is remote from C10 and C11 (see structure **13** for numbering). Further support for these assignments followed from an analysis of the ^{1}H NMR spectrum of the derived γ-hydroxylated α,β-unsaturated enone **16** that was produced in 56% yield by treating epoxide **15** with lithium hexamethyldisilazide (LiHMDS). In particular, the signal attributed to H4 in the ^{1}H NMR spectrum of rearrangement product **16** appears as a doublet of doublets (J = 8.0 and 2.4 Hz) at δ_H 4.13 and the magnitude of the larger coupling is consistent with a relatively large dihedral angle (slightly less than 180°) between this proton and the vicinally related H4a. The 2.4 Hz coupling between the resonances due to H4 and H3 is suggestive of a smaller dihedral angle between these nuclei (*ca*. 100° as judged by inspection of molecular models) and provides further support for the illustrated α-orientation of the C4 hydroxyl group within allylic alcohol **16**. Final confirmation of the assigned structures of compounds **14**, **15** and **16** follows from single-crystal X-ray analyses of each of them. The relevant data are presented in the Experimental Section while the derived ORTEPs are shown in the SI.

In the next step of the reaction sequence, enone **16** was reacted with the Gilman reagent[14] generated *in situ* from cuprous iodide and methyllithium and thereby affording *ent*-8-deoxydihydrotsugicoline (*ent*-**1**) in 56% yield. The assigned structure follows from the derived spectral data and, as shown in Table 1, a comparison of the ^{13}C and ^{1}H NMR data recorded on the synthetic material with those reported[3b] for the natural product 8-deoxydihydrotsugicoline (**1**) revealed an excellent match. The specific rotation of the synthetically derived material was –24.0 (c = 2.4, methanol) while that reported[3b] for the

natural product was +19 (c = 0.13, methanol) and thus indicating that the two compounds are enantiomerically related.

Table 1: *Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically-derived Compound* ent-***1*** *with those Reported for 8-Deoxydihydrotsugicoline (**1**).*

^{13}C NMR Data for Compound **1** (δ_C)[a]	^{13}C NMR Data for Compound *ent*-**1** (δ_C)[b]	^{1}H NMR Data for Compound **1** (δ_H)[c]	^{1}H NMR Data for Compound *ent*-**1** (δ_H)[d]
210.7	210.4	3.04, t, J = 10.5 Hz, 1H	3.05, t, J = 10.4 Hz, 1H
75.4	75.2	3.01, dd, J = 16.1 and 2.2 Hz, 1H	3.02, dd, J = 15.9 and 2.2 Hz, 1H
71.9	71.8	2.59, dd, J = 16.1 and 4.7 Hz, 1H	2.59, dd, J = 15.9 and 4.8 Hz, 1H
58.4	58.4	2.52, ddd, J = 9.7, 4.7 and 2.2 Hz, 1H	2.52, ddd, J = 9.7, 4.8 and 2.2 Hz, 1H
48.2	48.1	2.38, dt, J = 10.6 and 8.2 Hz, 1H	2.39, dt, J = 10.6 and 8.1 Hz, 1H
46.4	46.3	2.06, dddd, J = 10.5, 8.2, 7.1 and 6.8 Hz, 1H	2.06, m, 1H
45.9	45.8	1.69, ddd, J = 13.1, 7.1 and 1.1 Hz, 1H	1.69, dd, J = 13.2 and 7.2 Hz, 1H
44.1	44.1	1.62, dd, J = 13.1 and 6.8 Hz, 1H	1.66–1.54, complex m, 3H
38.4	38.3	1.60, m, 1H	–
38.0	37.9	1.59, m, 1H	–
31.5	31.5	1.49, dd, J = 13.0 and 10.6 Hz, 1H	1.49, dd, J = 12.9 and 10.5 Hz, 1H
31.0	31.0(3)	1.23, s, 3H	1.23, s, 3H
31.0	30.9(7)	1.13, s, 3H	1.13, s, 3H
27.2	27.3	1.06, d, J = 6.5 Hz, 3H	1.06, d, J = 6.5 Hz, 3H
18.4	18.4	1.03, s, 3H	1.03, s, 3H
–	–	signal due to hydroxyl group proton not observed	signal due to hydroxyl group proton not observed

[a] data obtained from reference 3b - recorded in CD_3OD at either 150 or 100 MHz; [b] data recorded in CD_3OD at 100 MHz; [c] data obtained from reference 3b - recorded in CD_3OD at either 600 or 400 MHz; [d] data recorded in CD_3OD at 400 MHz.

Reduction of compound *ent*-**1** using sodium bis(2-methoxyethoxy)aluminium hydride afforded a chromatographically separable mixture of the corresponding and crystalline cyclobutanols *ent*-radudiol (*ent*-**2**) (41%) and **17** (53%). Single-crystal X-ray analysis were carried out on both of these products and the derived ORTEPs together with selected crystallographic data are provided in the SI and Experimental section,

respectively. Once again, a comparison (Table 2) of the ^{13}C and ^{1}H NMR data derived from compound *ent*-**2** with those reported[3a] for the natural product radudiol (**2**) revealed an excellent match.

Table 2: *Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically-derived Compound* ent-***2*** *with those Reported for Radudiol (**2**).*

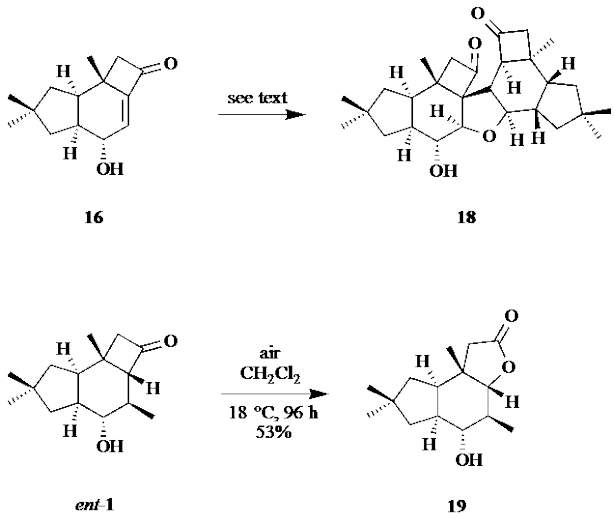
^{13}C NMR Data for Compound **2** (δ_C)[a]	^{13}C NMR Data for Compound *ent*-**2** (δ_C)[b]	^{1}H NMR Data for Compound **2** (δ_H)[c]	^{1}H NMR Data for Compound *ent*-**2** (δ_H)[d]
76.3	76.5	3.98, ddd, *J* = 7, 7 and 7 Hz, 1H	4.01, q, J = 7.0 Hz, 1H
71.3	71.8	3.16, dd, *J* = 10.8 and 9.6 Hz, 1H	3.17, dd, *J* = 10.9 and 9.4 Hz, 1H
60.7	61.1	2.36, ddd, *J* = 10, 9 and 8 Hz, 1H	2.35, dt, *J* = 10, 8 and 8.5 Hz, 1H
48.0	48.2	2.14, dd, *J* = 11.4 and 7.4 Hz, 1H	2.16, dd, *J* = 11.6 and 7.3 Hz, 1H
46.4	46.4	2.12, dddd, *J* = 11, 11, 10 and 7 Hz, 1H	2.09, tdd, *J* = 11.0, 9.5 and 7.0 Hz, 1H
44.6	44.8	1.77, dd, *J* = 12.2 and 6.8 Hz, 1H	1.73, ddd, *J* = 12.1, 6.8 and 1.5 Hz, 1H
43.7	44.1	1.70, dd, *J* = 8 and 7 Hz, 1H	1.67, t, *J* = 7.2 Hz, 1H
41.2	41.6	1.54, dd, *J* = 13.4 and 9.0 Hz, 1H	1.57-1.34, complex m, 4H
41.4	41.4	1.50, m, 1H	–
38.4	38.7	1.48, dd, *J* = 11.4 and 7.1 Hz, 1H	–
31.0	31.2	1.42, dd, *J* = 13.4 and 8.0 Hz, 1H	–
29.6	29.8	1.25, dd, *J* = 12 and 11 Hz, 1H	1.22, t, *J* = 11.9 Hz, 1H
28.7	28.9	1.11, d, *J* = 6.5 Hz, 3H	1.09, d, *J* = 6.4 Hz, 3H
28.6	28.8	1.12, s, 3H	1.08, s, 3H
18.0	18.1	1.08, s, 3H	1.07, s, 3H
–	–	1.01, s, 3H	0.97, s, 3H
–	–	signals due to hydroxyl group protons not observed	signals due to hydroxyl group protons not observed

[a] data obtained from reference 3a - recorded in $CDCl_3$ at 125 MHz; [b] data recorded $CDCl_3$ at 100 MHz; [c] data obtained from reference 3a - recorded in $CDCl_3$ at 500 MHz; [d] data recorded in $CDCl_3$ at 400 MHz.

The specific rotation of the synthetically derived material was –24 (*c* 1.0, $CHCl_3$) while that reported[3a] for the natural product is +27 (*c* = 1.0, $CHCl_3$) and thus indicating that the two compounds are also enantiomerically related.

Methylenecyclobutanone **16** and derivative *ent*-**1** each displayed unanticipated reactivities that are worth noting. Thus, as shown in Scheme 2, on treating the former compound with the Gilman reagent, so as to generate the conjugate addition product *ent*-**1**, varying quantities (see Experimental) of the chromatographically separable and crystalline hetero-dimer **18** were also observed. Compound **18**, the structure of which was confirmed by single-crystal X-ray analysis, presumably arises through sequential hetero-Michael/Michael addition reactions of monomer **16**.[15] Cyclobutanone *ent*-**1**, on the other hand, was observed to engage in a regioselective Baeyer-Villiger-type oxidation reaction on exposure to air for extended periods of time and so affording lactone **19**. The structure of this last compound was also confirmed by single-crystal X-ray analysis. The conversion *ent*-**1** $\rightarrow$ **19** raises the possibility that the enantiomer of the latter compound (*viz*. *ent*-**19**) could be encountered in extracts of the organism producing 8-deoxydihydrotsugicoline (**1**).

Scheme 2



CONCLUSION

The present work serves to highlight the utility of the readily available, stereochemically defined and enantiomerically pure metabolite **3** as a starting material in the chemical synthesis of either enantiomeric form of the protoilludane framework. Which form is accessed is dictated by the facial selectivity of the Diels-Alder reaction that this cyclic diene or its derivatives engage in.[16] Thus, the high pressure-promoted cycloaddition reaction of compound **3** itself with dienophiles such as cyclopentenone (**4**) results in preferential *s* *addition* (relative to the hydroxyl groups of the diene) and the formation of adducts that can be elaborated to the natural enantiomeric form of the protoilludane framework.[5b] In contrast, the acetonide derivative, **5**, of metabolite **3** readily participates in a thermally induced Diels-Alder reaction that proceeds with *a* *selectivity* so as to generate an adduct that can be elaborated, as shown above, to the non-natural enantiomeric form of the protoilludane framework. The adducts in both enantiomeric series are themselves readily converted, through straightforward manipulations of the diol

residue, into the corresponding cyclopentannulated bicyclo[2.2.2]oct-5-en-2-ones that then participate in a photochemically-promoted 1,3-acyl migration reaction (Givens rearrangement) and so affording the protoilludane framework. In principle, the functionality embodied in both the intitially produced Diels-Alder adducts and the derived photoproducts allows for their manipulation in ways relevant to the total synthesis of many other protoilludanes as well as a range of analogues. Work directed towards such ends continues in our laboratories.

EXPERIMENTAL SECTION

General Protocols.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. Infrared spectra (ν_{max}) were recorded on a FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and

are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL), potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL)), *p*-anisaldehyde or vanillin: sulfuric acid (conc.): ethanol (15 g : 2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[17] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents and other inorganic salts were generally commercially available and were used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[18] Where necessary, reactions were performed under an nitrogen atmosphere.

Specific Chemical Transformations.

Compound 7. A magnetically stirred solution of the *β*-epimeric form of alcohol **6**[8] **(**240 mg, 0.86 mmol) in THF (8.5 mL) maintained at 0 °C was treated with sodium hydride (106 mg of a 60% dispersion in mineral oil, 4.42 mmol). The ensuing mixture was heated under reflux for 6 h before being cooled to room temperature then treated, rapidly, with carbon disulfide (0.52 mL, 8.63 mmol). After 11 h the reaction mixture was again heated under reflux, this time for 2 h, before being cooled to room temperature and treated with iodomethane (0.59 mL, 9.48 mmol). After 2 h the reaction mixture was, once

again, heated under reflux, this time for 6 h, then cooled to room temperature and quenched with acetic acid (0.3 mL). The ensuing mixture was filtered through a pad of diatomaceous earth and the filtrate washed with ethyl acetate (4 x 10 mL). The combined filtrates were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica, 0:1 → 1:9 *v/v* ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.4) gave a white solid. Recrytallization (hexane) of this material afforded the β-epimeric form of xanthate **7** (220 mg, 69%) as a white-off, crystalline solid, mp = 195-196 °C, $[\alpha]^{25}_D$ = +36.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (dd, *J* = 6.0 and 1.1 Hz, 1H), 5.92–5.87 (complex m, 2H), 4.24 (dd, *J* = 7.2 and 3.2 Hz, 1H), 3.82 (d, *J* = 7.2 Hz, 1H), 2.82–2.77 (complex m, 1H), 2.58 (s, 3H), 2.27 (m, 1H), 2.17 (dd, *J* = 10.4 and 6.0 Hz, 1H), 1.47 (ddd, *J* = 11.9, 7.2 and 1.0 Hz, 1H), 1.39 (t, *J* = 11.9 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.1, 137.3, 125.9, 109.1, 90.8, 83.9, 79.9, 50.1, 46.0, 42.2, 40.5, 40.0, 37.8, 25.5, 25.1, 22.5, 19.7, 19.0 (one signal obscured or overlapping); IR ν_{max} 2967, 2930, 2895, 2885, 1454, 1378, 1365, 1281, 1260, 1229, 1192, 1164, 1081, 1068, 1055, 1037, 1012, 890, 742 cm^{-1}; MS (EI, 70 eV) *m/z* 368 ($M^{+\bullet}$, 58%), 353 [$(M - CH_3\bullet)^+$, 48], 321 (18), 268 (25), 203 (45), 202 (58), 160 (100), 145 (63), 105 (67), 95 (93), 91 (78); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{19}H_{28}O_3S_2$, 368.1480; found, 368.1480.

Subjection of the α-epimeric form of alcohol **6**[8] to the above-mentioned reaction conditions afforded a dark residue on work up. Flash column chromatographic purification of this material (silica, 0:1 → 1:9 *v/v* ethyl acetate/hexane gradient elution)

and concentration of the appropriate fractions (R_f = 0.5) afforded a white solid. Recrystallization (diethyl ether) of this material afforded the α-epimeric form of xanthate **7** (87%) as a white, crystalline solid, mp = 140-141 °C, $[\alpha]^{25}_D$ = −10.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (ddd, *J* = 8.3, 6.3 and 1.2 Hz, 1H), 5.86 (dq, *J* = 8.3 and 1.2 Hz, 1H), 5.65 (d, *J* = 8.4 Hz, 1H), 4.23 (ddd, *J* = 7.3, 3.3 and 1.2 Hz, 1H), 3.82 (dd, *J* = 7.2 and 1.2 Hz, 1H), 2.72–2.69 (complex m, 1H), 2.56 (s, 3H), 2.31 (m, 1H), 2.02 (dd, *J* = 10.8 and 8.9 Hz, 1H), 1.57 (dd, *J* = 12.8 and 8.0 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.20–1.25 (complex m, 1H), 1.17 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.9, 135.8, 131.0, 109.0, 90.8, 82.9, 79.5, 48.9, 43.6, 42.0, 40.6, 38.8, 37.6, 26.6, 25.5, 25.0, 22.6, 18.9, 18.8; IR ν_{max} 2962, 2935, 2888, 1463, 1375, 1256, 1207, 1166, 1057, 966, 886, 735, 719 cm^{-1}; MS (EI, 70 eV) *m/z* 353 [$(M - CH_3\bullet)^+$, 25%], 202 (100), 187 (96), 160 (80), 145 (78), 105 (45), 95 (70), 91 (65); HRMS (EI, 70 eV) $(M - CH_3\bullet)^+$ calcd for $C_{18}H_{25}O_3S_2$, 353.1245; found, 353.1248.

Compound 8. A magnetically stirred solution of β-epimeric form of xanthate **7** (6.20 g, 16.84 mmol) and AIBN (39 mg, 0.24 mmol) in toluene (230 mL) was treated, in one portion, with tri-*n*-butyltin hydride (13.8 mL, 51.36 mmol) and the resulting solution was stirred at 100 °C for 16 h. The cooled reaction mixture was treated with additional tri-*n*-butyltin hydride (9.2 mL, 34.24 mmol) and AIBN (58 mg, 0.35 mmol) and the resulting mixture heated under reflux for 1 h. The cooled reaction mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 0:1 $\rightarrow$ 1:49 *v/v* ethyl acetate/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.5 in 1:9 *v/v* ethyl acetate/hexane) afforded the title acetonide **8** (3.87 g, 87%) as a clear, colorless oil, $[\alpha]^{25}_D$ = +1.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 5.99 (dd, J = 8.2 and 6.4 Hz, 1H), 5.73 (dd, J = 8.2 and 1.2 Hz, 1H), 4.21 (dd, J = 7.2 and 3.2 Hz, 1H), 3.82 (dd, J = 7.2 and 1.2 Hz, 1H), 2.71 (dt, J = 6.2 and 2.9 Hz, 1H), 2.17 (m, 1H), 1.82 (m, 1H), 1.45–1.23 (complex m, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.16 (s, 3H), 1.05–0.90 (complex m, 2H), 0.96 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 130.3, 108.6, 83.7, 79.9, 45.4, 44.9, 43.2, 41.4, 40.5, 39.6, 38.9, 28.4, 27.7, 25.6, 25.0, 19.9; IR ν_{max} 2953, 2931, 2872, 2895, 1459, 1377, 1274, 1255, 1207, 1166, 1078, 1066, 1029, 895, 879, 850, 826, 733, 707 cm^{-1}; MS (EI, 70 eV) *m/z* 247 [(M – CH_3•)$^+$, 27%], 204 (80), 162 (100); HRMS (EI, 70 eV) (M – CH_3•)$^+$ calcd for $C_{16}H_{23}O_2$, 247.1698; found, 247.1704.

Treatment of the α-epimeric form of xanthate **7** in the same way as described immediately above for the corresponding β-epimer afforded, after work-up and flash chromatography, compound **8** (89%, 23 mmol scale) as a clear, colorless oil. This material was identical, in all respects, with that obtained by reduction of the major epimeric form of compound **7**.

Compound 9. A magnetically stirred solution of acetonide **8** (2.09 g, 7.98 mmol) in methanol/water (120 mL of a 5:1 *v/v* mixture) was treated with DOWEX-50 resin (4.07 g of the acidified form). The ensuing mixture was heated at 70 °C for 72 h then cooled and the resin removed by filtration and washed with methanol (3 × 50 mL). The combined filtrates were concentrated under reduced pressure and the residue diluted with brine (10 mL) then extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the residue thus obtained subjected to column chromatography (silica, 1:20 → 1:1 *v/v* ethyl acetate/hexane gradient elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 3:7 *v/v* ethyl acetate/hexane) afforded the starting acetonide **8** (550 mg, 26% recovery) that was identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.8 in 3:7 *v/v* ethyl acetate/hexane) afforded a solid that on recrystallization (hexane) afforded diol **9** (940 mg, 72% or 97% brsm) as a white, crystalline solid, mp = 84–85 °C, $[\alpha]^{25}_D$ = −11.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 8.2 and 6.4 Hz, 1H), 5.86 (dd, *J* = 8.2 and 1.4 Hz, 1H), 3.89 (dd, *J* = 7.5 and 2.8 Hz, 1H), 3.46 (dd, *J* = 7.5 and 1.2 Hz, 1H), 2.69 (m, 1H), 2.25–2.18 (complex m, 3H), 1.89 (td, *J* = 10.3 and 7.7 Hz, 1H), 1.43 (m, 2H), 1.18 (s, 3H), 1.04–0.87 (complex m, 2H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 131.9, 75.2, 71.8, 46.3, 45.0, 43.9, 43.0, 41.8, 41.0, 38.9, 28.4, 27.7, 19.6; IR ν_{max} 3369, 2951, 2928, 2869, 1459, 1365, 1118, 1077, 1053, 1031, 1014, 807, 731, 707 cm^{-1}; MS (EI, 70 eV) *m/z* 222 ($M^{+\bullet}$, <1%), 162 (95), 147 (43), 106 (45), 86 (72), 84 (100); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{14}H_{22}O_2$, 222.1620; found, 222.1626.

Compound 10. A magnetically stirred solution of diol **9** (1.09 g, 4.91 mmol) and *p*-TsOH•H_2O (2.05 g, 10.8 mmol) in dichloromethane (90 mL) was cooled to 0 °C and 4-acetamido-TEMPO (2.30 g, 10.8 mmol) was added in portions over 2 h. Stirring of the ensuing mixture was continued for 2 h then it was quenched with $NaHCO_3$ (100 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, 1:9 *v/v* ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 3:7 *v/v* ethyl acetate/hexane), a

white solid that upon recrystallization (ethyl acetate) gave acyloin **10** (972 mg, 90%), as a white, crystalline solid mp = 86–87 °C, $[\alpha]^{25}_{D}$ = +202.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (t, *J* = 7.6 Hz, 1H), 6.02 (d, *J* = 7.6 Hz, 1H), 3.38 (s, 1H), 3.11 (dd, *J* = 6.5 and 2.5 Hz, 1H), 2.63 (m, 1H), 2.27 (td, *J* = 10.4 and 7.4 Hz, 1H), 1.55 (m, 2H), 1.25 (s, 3H), 1.08 (m, 2H), 1.00 (s, 3H), 0.93 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 211.9, 140.3, 126.5, 75.0, 51.1, 47.7, 44.9, 44.7, 43.6, 39.1, 38.9, 28.3, 27.6, 18.3; IR ν_{max} 3418, 2947, 2931, 2898, 2853, 1727, 1457, 1402, 1381, 1365, 1270, 1210, 1136, 1079, 1035, 993, 789, 764, 713, 655 cm^{-1}; MS (EI, 70 eV) *m/z* 220 ($M^{+\bullet}$, 100%), 205 (33), 192 (25), 163 (80), 161 (62), 147 (48), 107 (55), 105 (60), 91 (70); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{14}H_{20}O_2$, 220.1463; found, 220.1465.

Compound 11. A magnetically stirred solution of acyloin **10** (938 mg, 4.26 mmol) in dichloromethane (70 mL) maintained at 0 °C was treated, in portions and successively, with triethylamine (13.3 mL, 96.0 mmol), benzoyl chloride (1.2 mL, 10.2 mmol) and DMAP (1.72 g, 14.1 mmol). The ensuing mixture was stirred at 18 °C for 16 h then quenched with HCl (200 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (3 x 100 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica, 1:9 *v/v* ethyl acetate/hexane elution) to give, after concentration of the appropriate fractions (R_f = 0.8 in 1:4 *v/v* ethyl acetate/hexane) a white solid. Recrystallization of this material (dichloromethane) afforded compound **11** (1.24 g, 90%) as a white, crystalline solid, mp = 82–83 °C; $[\alpha]^{25}_{D}$ = +135.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$*) δ* 8.03–7.99

(complex m, 2H), 7.58–7.53 (complex m, 1H), 7.44–7.40 (complex m, 2H), 6.21 (t, J = 7.2 Hz, 1H), 6.12 (d, J = 7.2 Hz, 1H), 5.13 (s, 1H), 3.18 (dd, J = 6.6 and 2.6 Hz, 1H), 2.79–2.70 (complex m, 1H), 2.47 (m, 1H), 1.63–1.54 (complex m, 3H), 1.18–1.05 (complex m, 1H), 1.14 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 166.2, 139.4, 133.2, 129.9, 129.5, 128.3, 127.0, 74.5, 51.8, 47.3, 44.7, 43.9, 43.8, 39.3, 39.2, 28.2, 27.6, 18.4; IR ν_{max} 2953, 2861, 1742, 1724, 1269, 1111, 1070, 1028, 708 cm^{-1}; MS (EI, 70 eV) *m/z* 324 ($M^{+\bullet}$, 2%), 202 (35%), 162 (40), 106 (35), 105 (100); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{21}H_{24}O_3$, 324.1725; found, 324.1732.

Compound 12. A magnetically stirred solution of benzoate **11** (1.20 g, 3.70 mmol) in THF/methanol (55 mL of a 2:1 *v/v* mixture) was cooled to −78 °C then SmI_2 (*ca*. 150 mL of a 0.1 M solution in THF) was added dropwise until complete consumption of starting material was observed (as determined by TLC). The ensuing mixture was stirred at −78 °C for a further 0.25 h then poured directly into saturated K_2CO_3 (100 mL of a saturated solution) and the mixture thus formed extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with brine (1 x 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 3:97 *v/v* ethyl acetate/hexane elution) to afford, after concentration of the relevant fractions (R_f = 0.4 in 1:9 *v/v* ethyl acetate/hexane), compound **12** (604 mg, 80%) as a clear, colorless oil, $[\alpha]^{25}_D$ = +196.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13–6.07 (complex m, 2H), 3.02 (dt, J = 5.2 and 2.4 Hz, 1H), 2.63 (m, 1H), 2.25 (m, 1H), 1.88 (ABq, J = 18.1 Hz, 2H), 1.50–1.43 (complex m, 2H), 1.16 (s, 3H), 1.12–1.05 (complex m, 2H), 0.98 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 141.4, 127.7, 53.4, 49.7, 46.9,

44.5, 44.4, 42.0, 40.4, 39.4, 28.4, 27.7, 22.2; IR ν_{max} 3037, 2953, 2869, 1729, 1458, 1405, 1382, 1366, 1264, 1202, 1091, 912, 799, 715 cm^{-1}; MS (EI, 70 eV) *m/z* 204 ($M^{+\bullet}$, 20%), 163 (25), 162 (100), 147 (45), 106 (45), 91 (40); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1518.

Compound 13. A magnetically stirred solution of ketone **12** (100 mg, 0.49 mmol) in deoxygenated and dry dichloromethane (15 mL) was irradiated for 14 h at 5 °C using a standard (125 W) high-pressure mercury lamp (CAUTION – avoid eye contact with illuminated lamp) equipped with water-jacketed cooling system so as to maintain the required reaction temperature. The reaction mixture was then concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 1:49 *v/v* ether/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5 in 1:9 *v/v* ethyl acetate/hexane) afforded cyclobutanone **13** (28 mg, 28% or 54% brsm) as a clear, colorless oil, $[\alpha]^{25}_D = -607.0$ (*c* 1.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (d, *J* = 10.0 Hz, 1H), 5.50 (ddd, *J* = 10.0, 5.2 and 2.8 Hz, 1H), 3.17 (m, 1H), 3.03 (dd, *J* = 16.4 and 2.4 Hz, 1H), 2.67–2.60 (complex m, 1H), 2.52 (dd, *J* = 16.4 and 5.6 Hz, 1H), 2.33 (dt, *J* = 14.0 and 7.2 Hz, 1H), 1.88 (dd, *J* = 14.0 and 8.4 Hz, 1H), 1.55-1.43 (complex m, 2H), 1.23 (s, 3H), 1.13 (t, *J* = 12.5 Hz, 1H), 1.03 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 133.8, 118.6, 62.5, 55.5, 47.5, 43.3, 43.0, 38.6, 38.0, 32.1, 32.0, 29.9, 26.4; IR ν_{max} 3018, 2951, 2927, 2866, 1781, 698 cm^{-1}; MS (EI, 70 eV) *m/z* 204 ($M^{+\bullet}$, 1%), 162 (100), 147 (72), 106 (75), 105 (45), 91 (68); HRMS (EI, 70 eV) $M^{+\bullet}$ calcd for $C_{14}H_{20}O$, 204.1514; found, 204.1514.

Concentration of fraction B (R_f = 0.4 in 1:9 *v/v* ethyl acetate/hexane) afforded starting material **12** (49 mg, 49% recovery) as a clear, colorless oil that proved identical, in all respects, with authentic material.

Compounds 14 and 15. A magnetically stirred solution of cyclobutanone **13** (57 mg, 0.28 mmol) in acetone (1.0 mL) maintained under nitrogen was cooled to 0 °C then treated, dropwise, with dimethyldioxirane[13] (*ca.* 8.3 mL of a 0.034 M solution in acetone, 0.28 mmol). The ensuing mixture was stirred at 0 °C for 4 h then concentrated under reduced pressure. The resulting clear, colorless oil was subjected to flash chromatography (silica, 1:19 *v/v* ethyl acetate/hexane elution) and so affording two fractions, A and B.

Concentration of fraction A [R_f = 0.5(1) in 1:4 *v/v* ethyl acetate/hexane] afforded a white solid. Recrystallization (pentane) of this material afforded epoxide **14** (11 mg, 18%) as a white, crystalline solid, mp = 44–46 °C, $[\alpha]^{25}_D$ = −214 (*c* 2.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.16 (m, 1H), 3.11–3.02 (complex m, 3H), 2.61–2.50 (complex m, 2H), 2.23 (dt, *J* = 13.9 and 7.2 Hz, 1H), 1.88 (dd, *J* = 13.6 and 9.2 Hz, 1H), 1.71 (dd, *J* = 13.6 and 3.0 Hz, 1H), 1.50 (dd, *J* = 13.3 and 11.8 Hz, 1H), 1.32 (dd, *J* = 11.8 and 6.9 Hz, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 61.2, 57.2, 56.9, 52.0, 45.1, 44.6, 44.5, 37.2, 34.7, 31.4, 30.2, 29.7, 27.0; IR ν_{max} 2950, 2630, 2865, 1779 cm^{-1}; MS (ESI, +ve) *m/z* 285 [$(M + Na + MeCN)^+$, 100%], 243 [$(M + Na)^+$, 85], 221 [$(M + H)^+$, 47]; HRMS (ESI, +ve) $(M + H)^+$ calcd for $C_{14}H_{21}O_2$, 221.1542; found, 221.1535.

Concentration of fraction B [R_f = 0.4(6) in 1:4 *v/v* ethyl acetate/hexane] afforded a white solid. Recrystallization (pentane) of this material afforded epoxide **15** (35 mg, 57% yield) as a white, crystalline solid, mp = 40–41 °C, $[\alpha]^{25}_D$ = −135 (*c* 4.8, $CHCl_3$). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 3.28 (dd, J = 5.8 and 3.6 Hz, 1H), 2.92–2.84 (complex m, 2H), 2.88 (dd, J = 5.8 and 2.1 Hz, 1H), 2.38 (m, 1H), 2.27 (dd, J = 16.6 and 6.2 Hz, 1H), 2.13 (m, 1H), 1.85 (dd, J = 13.7 and 8.5 Hz, 1H), 1.53 (dd, J = 13.7 and 2.6 Hz, 1H), 1.47 (dd, J = 12.7 and 6.6 Hz, 1H), 1.09 (s, 3H), 0.97 (s, 3H), 0.97 (t, J = 12.7 Hz, 1H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 58.7, 57.9, 55.5, 50.5, 46.3, 44.3, 41.5, 36.5, 36.4, 31.0, 30.7, 28.5, 27.3; IR ν_{max} 2950, 2929, 2867, 1783 cm^{-1}; MS (ESI, +ve) *m/z* 284 [$(M + Na + MeCN)^+$, 100%], 243 [$(M + Na)^+$, 25], 221 [$(M + H)^+$, 5]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{14}H_{20}NaO_2$, 243.1361; found, 243.1365.

Compound 16. A magnetically stirred solution of epoxide **15** (1.10 g, 5.4 mmol) in THF (54 mL) maintained under nitrogen was cooled to −78 °C then LiHMDS (6.5 mL of a 1.0 M solution in THF, 6.5 mmol) was added dropwise. The ensuing mixture was allowed to warm to 18 °C over 16 h before being quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with brine (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 1:19 → 1:5 *v/v* ethyl acetate/hexane gradient elution) and two fractions, A and B, thereby obtained.

Concentration of fraction A (R_f = 0.6 in 3:7 *v/v* ethyl acetate/hexane) afforded the starting epoxide **15** (431 mg, 39% recovery) which proved identical, in all respects, with authentic material.

Concentration of fraction B (R_f = 0.3 in 3:7 *v/v* ethyl acetate/hexane) afforded a white solid, recrystallization (pentane) of which gave title compound **16** (616 mg, 56%) as a white, crystalline solid, mp = 80–81 °C, $[\alpha]^{25}_D$ = +368 (*c* 1.1, $CHCl_3$). ^1H NMR (400

MHz, $CDCl_3$) δ 6.39 (d, J = 2.2 Hz, 1H), 4.13 (dd, J = 8.0 and 2.2 Hz, 1H), 3.57 (broad s, 1H), 2.70 (ABq, J = 16.9 Hz, 2H), 2.40–2.27 (complex m, 2H), 1.81 (dd, J = 12.5 and 5.5 Hz, 1H), 1.51–1.44 (complex m, 1H), 1.42–1.34 (complex m, 1H), 1.15 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 155.8, 132.8, 72.7, 60.9, 52.1, 46.5, 46.1, 41.0, 40.2, 36.9, 29.4, 26.8, 20.2; IR ν_{max} 3428, 2951, 2866, 1748, 1734, 1657, 1464, 1199, 1142, 1094, 854, 844 cm^{-1}; MS (ESI, +ve) *m/z* 462 [$(2M + Na)^+$, 55%], 413 (100), 275 [$(M + Na + CH_3OH)^+$, 51], 243 [$(M + Na)^+$,49]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{14}H_{20}NaO_2$, 243.1361; found, 243.1362.

Compounds *ent*-1 and 18. A magnetically stirred solution of CuI (1.66 g, 8.73 mmol) in THF (8.7 mL) maintained at 0 °C was treated with MeLi (11.0 mL of a 1.6 M solution in diethyl ether, 17.5 mmol) and the resulting mixture stirred at this temperature for 0.75 h. A solution of compound **16** (640 mg, 2.91 mmol) in THF (29 mL) was then added, dropwise, to the colorless reaction mixture and stirring continued at 0 °C for further 1 h. The ensuing mixture was quenched with NH_4Cl (100 mL of a saturated aqueous solution) and extracted with diethyl ether (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light yellow oil was subjected to flash chromatography (silica, 3:17 *v/v* ethyl acetate/hexane elution) to afford two fractions, A and B.

Concentration of fraction A [R_f = 0.4(2) in 3:7 *v/v* ethyl acetate/hexane] afforded a white solid, recrystallization (chloroform/hexanes) of which afforded compound **18** (198 mg, 31%) as a colorless, crystalline solid, mp = 213–215 °C, $[\alpha]^{25}_D$ = +74 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85–3.75 (complex m, 2H), 3.40 (dt, J = 8.6 and 2.0 Hz, 1H), 3.35 (dd, J = 11.2 and 9.3 Hz, 1H), 3.07 (d, J = 16.2 Hz, 1H), 2.76 (dd,

J = 16.2 and 2.2 Hz, 1H), 2.60–2.50 (complex m, 2H), 2.32 (dt, *J* = 12.3 and 7.0 Hz, 1H), 2.21–2.03 (complex m, 3H), 1.88–1.72 (complex m, 2H), 1.67–1.54 (complex m, 3H), 1.51–1.39 (complex m, 2H), 1.37 (s, 3H), 1.32 (s, 3H), 1.27–1.19 (complex m, 2H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.96 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 205.9, 83.9, 82.6, 73.5, 73,1, 65.8, 59.0, 57.8, 47.2, 46.3, 44.6, 44.2, 43.6, 43.4, 42.8(0), 42.7(8), 41.0, 39.0, 37.2, 35.3, 32.3, 32.0, 31.7, 29.5, 28.5, 26.8, 23.1; IR ν_{max} 3414, 2948, 2902, 2863, 1773, 1453, 1386, 1363, 1200, 1076, 1049, 1028 cm^{-1}; MS (ESI) *m/z* 463 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for . $C_{28}H_{40}NaO_4$, 463.2824; found, 463.2822.

Concentration of fraction B [R_f = 0.4(0) in 3:7 *v/v* ethyl acetate/hexane] afforded *ent*-8-deoxydihydrotsugicoline (*ent*-**1**) (384 mg, 56%) as a clear, colorless oil, $[\alpha]^{25}_D$ = −24 (*c* 2.4, methanol), $[\alpha]^{25}_D$ = −3.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (t, *J* = 10.3 Hz, 1H), 2.98 (dd, *J* = 16.0 and 2.2 Hz, 1H), 2.55 (dd, *J* = 16.0 and 4.8 Hz, 1H), 2.48 (ddd, *J* = 9.6, 4.9 and 2.2 Hz, 1H), 2.34 (m, 1H), 2.04–1.91 (complex m, 1H), 1.66 (dd, *J* = 12.9 and 7.1 Hz, 1H), 1.63–1.51 (complex m, 3H), 1.39 (dd, *J* = 12.9 and 10.8 Hz, 1H), 1.23 (s, 3H), 1.13 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 3H) (signal due to hydroxyl group proton not observed); ^{1}H NMR (400 MHz, CD_3OD) δ see Table 1; ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 74.6, 70.4, 57.6, 46.8, 44.9, 44.5, 43.1, 37.5, 36.6, 31.1, 30.4, 29.9, 26.9, 17.8; ^{13}C NMR (100 MHz, CD_3OD) δ see Table 1; IR ν_{max} 3414, 2951, 2927, 2868, 1772, 1463, 1045 cm^{-1}; MS (ESI, +ve) *m/z* 259 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{15}H_{24}NaO_2$, 259.1674; found, 259.1674.

Compounds *ent*-2 and 17. A magnetically stirred solution of compound *ent*-**1** (48 mg, 0.20 mmol) in THF (20 mL) maintained under nitrogen was cooled to 0°C then treated, dropwise, with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al, 130 μL of a 60 wt. % solution in toluene, 0.40 mmol). The ensuing mixture was allowed to warm up to 18 °C over 1 h before being heated under reflux for 1 h. The cooled reaction mixture was quenched with HCl (10 of a 1 M aqueous solution) and extracted with diethyl ether (3 x 50 mL) and the combined organic phases washed with brine (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 *v/v* dichloromethane/methanol elution) and two fractions, A and B, collected.

Concentration of fraction A [R_f = 0.3(6) in 9:1 *v/v* dichloromethane/methanol] afforded a white solid, recrystallization (methanol) of which gave compound *ent*-**2** (21 mg, 41%) as a colorless, crystalline solid, mp = 135–136 °C, $[\alpha]^{25}_D$ = –24.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ see Table 2; ^{1}H NMR (400 MHz, CD_3OD) δ 3.90 (q, *J* = 7.1 Hz, 1H), 3.06 (dd, *J* = 11.0 and 9.6 Hz, 1H), 2.40 (m, 1H), 2.18–2.04 (complex m, 2H), 1.74 (ddd, *J* = 12.2, 6.9 and 1.5 Hz, 1H), 1.66 (t, *J* = 7.3 Hz, 1H), 1.53 (dd, *J* = 13.3 and 8.9 Hz, 1H), 1.50–1.43 (complex m, 3H), 1.23 (t, *J* = 12.0 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.99 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ see Table 2; ^{13}C NMR (100 MHz, CD_3OD) δ 77.2, 72.1, 62.2, 49.0, 47.9, 45.9, 44.4, 43.1, 42.4, 39.4, 32.2, 30.2, 29.3, 18.6 (one signal obscured or overlapping); IR ν_{max} 3324, 2951, 2926, 2867, 1463, 1376, 1363, 1316, 1262, 1224, 1133, 1102, 1080, 1054, 1033, 1015, 999 cm^{-1}; MS (ESI, +ve) *m/z* 261 [$(M + Na)^+$, 100%]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for

$C_{15}H_{26}NaO_2$, 261.1831; found, 261.1830.

Concentration of fraction B [R_f = 0.3(3) in 9:1 *v/v* dichloromethane/methanol] afforded a white solid that upon recrystallization (ethyl acetate) afforded the title compound **17** (25 mg, 53%) as a white, crystalline solid, mp = 153–155 °C, $[\alpha]^{25}_D$ = +45 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (q, *J* = 7.2 Hz, 1H), 3.08 (t, *J* = 10.4 Hz, 1H), 2.05 (dt, *J* = 13.4 and 6.7 Hz, 1H), 2.00 (dd, *J* = 10.8 and 7.2 Hz, 1H), 1.98 (d, *J* = 8.5 Hz, 1H), 1.95–1.67 (complex m, 6H), 1.56 (dd, *J* = 13.9 and 7.6 Hz, 1H), 1.39 (dd, *J* = 12.4 and 6.6 Hz, 1H), 1.24 (t, *J* = 12.9 Hz, 1H), 1.09 (s, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 1.02 (s, 3H), 0.97 (s, 3H); ^{1}H NMR (400 MHz, CD_3OD) δ 4.37 (m, 1H), 2.94–3.03 (complex m, 1H), 2.05 (dt, *J* = 6.6 and 6.4 Hz, 1H), 2.00 (dd, *J* = 10.3 and 8.5 Hz, 1H), 1.94–1.85 (complex m, 3H), 1.83–1.73 (complex m, 2H), 1.52 (dd, *J* = 13.9 and 7.6 Hz, 1H), 1.39 (dd, *J* = 12.4 and 6.7 Hz, 1H), 1.28 (t, *J* = 12.9 Hz, 1H), 1.10 (s, 3H), 1.03 (s, 3H), 0.99 (d, *J* = 5.3 Hz, 3H), 0.98 (s, 3H) (signals due to hydroxyl group protons not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.7, 64.8, 52.5, 48.4, 46.3, 43.6, 43.1, 42.7, 36.4, 34.6, 32.4, 31.8, 30.2, 26.8, 19.0; ^{13}C NMR (100 MHz, CD_3OD) δ 75.1, 65.0, 54.3, 50.1, 47.5, 44.6, 44.3, 42.8, 37.2, 35.7, 32.9, 32.5, 31.3, 27.3, 19.5; IR ν_{max} 3324, 2952, 2926, 2866, 1454, 1364, 1196, 1088, 1031 cm^{-1}; MS (ESI, +ve) *m/z* 261 [$(M + Na)^+$, 100%], 177 (10); HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{15}H_{26}NaO_2$, 261.1831; found, 261.1831.

Compound 19. A solution of compound *ent*-**1** in dichloromethane (24 mg in 10 mL) was left to evaporate over 4 days at 18 °C while being exposed to air. The residue thus obtained was subjected to flash chromatography (silica, 3:17 *v/v* ethyl acetate/hexane elution) and afforded, after concentration of the appropriate fractions (R_f = 0.5 in 3:7 *v/v*

ethyl acetate/hexane) a white solid. Recrystallization (dichloromethane) of this material gave lactone **19** (14 mg, 53%) as a white, crystalline solid, mp = 126–127 °C, $[\alpha]^{25}_{D}$ = –63.0 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (d, *J* = 9.9 Hz, 1H), 3.13 (t, *J* = 10.7 Hz, 1H), 2.68 (d, *J* = 16.9 Hz, 1H), 2.32 (m, 1H), 2.11 (d, *J* = 16.9 Hz, 1H), 1.98–1.90 (complex m, 1H), 1.80 (dd, *J* = 13.9 and 1.7 Hz, 1H), 1.62 (dd, *J* = 13.9 and 7.0 Hz, 1H), 1.55 (dd, *J* = 12.6 and 7.0 Hz, 1H), 1.43 (m, 1H), 1.30 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.13 (s, 6H), 1.03 (s, 3H) (signal due to hydroxyl group proton not observed); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 89.5, 72.9, 45.6, 45.1, 43.4, 43.0, 42.9, 41.7, 40.4, 36.4, 32.5, 32.0, 25.3, 15.1; IR ν_{max} 3427, 2950, 2929, 2869, 1763, 1455, 1159, 1050, 1001, 980 cm^{-1}; MS (ESI, +ve) *m/z* 527 [$(2M + Na)^+$, 53%], 275 [$(M + Na)^+$, 100]; HRMS (ESI, +ve) $(M + Na)^+$ calcd for $C_{15}H_{24}NaO_3$, 275.1623; found, 275.1620.

Crystallographic Studies

Crystallographic Data for Compound *ent*-2. $C_{15}H_{26}O_2$, *M* = 238.37, *T* = 150 K, hexagonal, space group $P6_5$, *Z* = 6, *a* = 21.353(3) Å, *c* = 5.8048(10) Å; *V* = 2292.1(6) Å^3, D_x = 1.036 g cm^{-3}, 1483 unique data ($2\theta_{max}$ = 143.4°), *R* = 0.081 [for 1113 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.190 (all data), *S* = 1.02.

Crystallographic Data for Compound 7 (β-epimer). $C_{19}H_{38}O_3S_2$, *M* = 368.56, *T* = 150 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 6.2794(1) Å, *b* = 13.2695(1) Å, *c* = 23.5284(2) Å; *V* = 1960.49(4) Å^3, D_x = 1.249 g cm^{-3}, 3887 unique data ($2\theta_{max}$ = 144.6°), *R* = 0.022 [for 3815 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.058 (all data), *S* = 1.01.

Crystallographic Data for Compound 14. $C_{14}H_{20}O_2$, *M* = 220.31, *T* = 150 K, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 5.8991(1) Å, *b* = 12.6249(1) Å, *c* =

16.8455(2) Å; V = 1254.58(3) Å^3, D_x = 1.166 g cm^{-3}, 2409 unique data ($2\theta_{max}$ = 144.6°), R = 0.029 [for 2409 reflections with $I > 2.0\sigma(I)$]; Rw = 0.075 (all data), S = 1.00.

Crystallographic Data for Compound 15. $C_{14}H_{20}O_2$, M = 220.31, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 7.0022(1) Å, b = 12.5744(1) Å, c = 14.0683(2) Å; V = 1238.69(3) Å^3, D_x = 1.181 g cm^{-3}, 2452 unique data ($2\theta_{max}$ = 144.4°), R = 0.025 [for 2398 reflections with $I > 2.0\sigma(I)$]; Rw = 0.066 (all data), S = 1.00.

Crystallographic Data for Compound 16. $C_{14}H_{20}O_2$, M = 220.31, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 8.3922(1) Å, b = 8.6217(1) Å, c = 17.1215(1) Å; V = 1238.83(2) Å^3, D_x = 1.181 g cm^{-3}, 2457 unique data ($2\theta_{max}$ = 144.8°), R = 0.026 [for 2433 reflections with $I > 2.0\sigma(I)$]; Rw = 0.068 (all data), S = 1.01.

Crystallographic Data for Compound 17. $C_{15}H_{26}O_2$, M = 238.37, T = 150 K, monoclinic, space group $C2$, Z = 12, a = 33.1997(4) Å, b = 9.6115(1) Å, c = 13.8952(2) Å; β = 99.7857(12)°; V = 4369.43(10) Å^3, D_x = 1.087 g cm^{-3}, 7638 unique data ($2\theta_{max}$ = 144.8°), R = 0.035 [for 7219 reflections with $I > 2.0\sigma(I)$]; Rw = 0.087 (all data), S = 1.00.

Crystallographic Data for Compound 18. $C_{28}H_{40}O_4$, M = 440.62, T = 150 K, monoclinic, space group $P2_1$, Z = 4, a = 6.5903(1) Å, b = 27.7886(4) Å, c = 13.8017(2) Å; β = 101.7474(15)°; V = 2474.64(6) Å^3, D_x = 1.183 g cm^{-3}, 9541 unique data ($2\theta_{max}$ = 144.6°), R = 0.038 [for 8925 reflections with $I > 2.0\sigma(I)$]; Rw = 0.087 (all data), S = 1.00.

Crystallographic Data for Compound 19. $C_{15}H_{24}O_3$, M = 252.35, T = 150 K, monoclinic, space group $P2_1$, Z = 4, a = 8.5891(2) Å, b = 16.7819(2) Å, c = 9.8613(1) Å; β = 95.8337(13)°; V = 1414.06(4) Å^3, D_x = 1.185 g cm^{-3}, 5477 unique data ($2\theta_{max}$ = 144.6°), R = 0.033 [for 5190 reflections with $I > 2.0\sigma(I)$]; Rw = 0.077 (all data), S = 0.99.

Structure Determinations. Images were measured on a CCD diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) and data extracted using the CrysAlis package.[19] Structure solution was by direct methods (SIR92).[20] The structures of compounds ***ent*-2**, **7** (β-epimer) and **14**-**19** were refined using the CRYSTALS program package.[21] Atomic coordinates, bond lengths and angles, and displacement parameters for compounds ***ent*-2**, **7** (β-epimer) and **14**-**19** have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1442299, 1442300, 1442301, 1442302, 1442303, 1442304, 144230 and 1442306). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds *ent*-**1,** *ent*-**2**, **7** (minor and major epimers) and **8**-**19** together with X-ray crystallographic data (CIFs) for compounds ***ent*-2**, **7** (β-epimer) and **14**-**19**. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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