Syntheses of Structurally and Stereochemically Varied Forms of C₇N Aminocyclitol Derivatives from Enzymatically-derived and Homochiral *cis*-1,2-Dihydrocatechols

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Supporting Information Placeholder

ABSTRACT: The structurally and stereoisomerically varied C₇N aminocyclitol derivatives **2-4** have been prepared, using a versatile and flexible range of protocols, from the *cis*-1,2-dihydrocatechols **5** and **6**, homochiral metabolites derived from the whole-cell biotransformation of the corresponding halobenzene. Reaction sequences that enable syntheses of the enantiomeric forms of these derivatives have also been established.

The C₇N aminocyclitols are microbially-derived and biologically active compounds that have been deployed in a number of therapeutic and agrochemical roles, either in their own right or as components of structurally more complex systems.¹ So, for example, they are used as agents for the treatment of bacterial infections, type-II diabetes and as antifungal agents to treat rice blight.¹ Given such pivotal activities and the emergence of resistance to their more heavily exploited forms,² efforts continue apace to identify new variants,³ to establish how they are produced in vivo⁴ and to develop syntheses of them and structural analogues.⁵ The 2015 report⁶ by Gademann and co-workers on the isolation of the C₇N aminocyclitol kirkamide (**1**) from an obligate leaf nodule symbiont of the Rubiaceae shrub *Psychotria kirkii* emphasizes the ongoing levels of interest in such systems. So, for example, various biological studies established that kirkamide is toxic to both aquatic arthropods and insects with the latter effect suggesting that the compound plays a protective (anti-feedant) role in the plant hosting the symbiont. The structure of kirkamide, which embodies a homoallylic rather than the normally located allylic nitrogen, was established by NMR spectroscopic methods and confirmed by single-crystal X-ray analysis. An eleven-step total synthesis of this natural product was established using methyl *N*-acetyl-*D*-glucosamine as starting material and employed a Ferrier carbocyclization⁷ for the pivotal ring-forming step.

Figure 1: The recently reported C₇N aminocyclitol kirkamide (**1**)

By virtue of their diverse biological activities and structural variations, there remains an intense interest in developing new methods for the synthesis of aminocyclitols, including C₇ variants.⁵ As part of our ongoing efforts in this area,^{5b} we now report syntheses of compounds such as 4-*epi*-kirkamide (**2**), the *ent*-kirkamide derivative **3** and the β,γ -unsaturated amide **4** from the homochiral *cis*-dihydrocatechols **5** and **6** that are, themselves, readily obtained through the whole-cell biotransformation of bromo- and iodo-benzene, respectively.⁸ Means for accessing the enantiomeric forms of these C₇N aminocyclitol derivatives are also described.

Figure 2: The structures of the target C_7N aminocyclitol derivatives **2-4** and the homochiral *cis*-1,2-dihydrocatechols **5** and **6** used as starting materials

The opening stages of the synthetic route to 4-epi-kirkamide (**2**) are shown in Scheme 1 and involve the ready and well-established conversion of diol **5** into the acetonide **7**.⁹ Subjection of the latter compound to reaction with *N*-bromoacetamide (NBA) in the presence of tin tetrachloride at $-40\text{ }^{\circ}\text{C}$ afforded, in both a regio- and diastereoselective manner, the anticipated and previously reported adduct **8**¹⁰ (77%), the structure of which was confirmed by single-crystal X-ray analysis (see Supporting Information – SI – for details). On treating bromoacetamide **8** with potassium hexamethyldisilazide (KHMDs) and tetra-*n*-butylammonium bromide (TBAB) under conditions similar to those defined by Hudlicky and co-workers for the formation of acylaziridine **9**,^{10b} then the oxazoline **10** was obtained in 39% yield. The structure of compound **10** follows from the derived spectroscopic data and the single-crystal X-ray analysis of a derivative (see below). Subjection of an authentic sample of compound **9**^{10b} to the reaction conditions just described also afforded the isomeric heterocycle **10**, an observation consistent with the behavior of other *N*-acyl aziridines.¹¹ The regioselectivity associated with the conversion **9** $\rightarrow$ **10** process (a Heine-type reaction¹¹) is intriguing and presumably the consequence of the mesomerically electron-donating properties of the flanking bromo-olefin subunit within the substrate. On treating compound **10** with aqueous acetic acid the associated oxazoline ring was cleaved and thereby affording the aminocyclitol **11** (48%) wherein the amine residue is in a homoallylic relationship with the cyclohexene double bond, as seen in kirkamide.

Scheme 1: Opening stages of the route to C_7N aminocyclitol **2**

The elaboration of compound **11** to target **2** requires the introduction of a hydroxymethyl group at the bromine-bearing carbon and we sought to do this using one of various possible palladium-catalyzed carbonylation processes.¹² Unfortunately, all such efforts proved unsuccessful and so bromide **11** was converted (Scheme 2) into the corresponding iodide **12** (81%) under Whitehead's conditions¹³ in the expectation that the latter would serve as a more effective cross-coupling partner. However, even the latter electrophile proved ineffective in this regard until we adapted a previously reported procedure¹⁴ allowing for the formation of the Weinreb amide **13** (95%). *O*-Silylation of this by now long-sought product was achieved under standard conditions using *tert*-butyldimethylsilyl chloride (TBS-Cl) and the resulting ether **14** (95%) subjected to reduction with lithium aluminium hydride, so forming, after work-up, the unsaturated aldehyde **15** (84%). Luche reduction¹⁵ of the last compound then afforded the hydroxymethylated product **16** (95%), the structure of which was confirmed by single-crystal X-ray analysis (see SI for details). Treatment of compound **16** with aqueous acetic acid at $60\text{ }^{\circ}\text{C}$ for 7 h then afforded target **2** (the *C*₄-epimer of kirkamide) (83%), the spectral data for which were in complete accord with the assigned structure.

Scheme 2: Closing stages of the route to target **2** (4-epi-kirkamide)

An alternate and more direct route to the kirkamide “scaffold” that allows for the creation of a *trans*-relationship between the amine residue and its neighbouring, homoallylic hydroxyl group, as seen in the natural product **1**, is shown in Scheme 3. This starts with the conversion of diol **6** into the known bromohydrin **17**¹⁶ (74%) and on treating the later with sodium methoxide the previously reported epoxide **18**¹⁶ (91%) was obtained. Compound **18** itself could be engaged in a two-fold Mitsunobu reaction using *p*-nitrobenzoic acid as the nucleophile and thus producing the bis-ester **19** (98%), treatment of which with potassium carbonate in methanol afforded the diol **20** (84%). On treating this last compound with freshly prepared *p*-toluenesulfonyl isocyanate (TsNCO) then reaction occurred selectively at the hydroxyl group remote from the iodinated carbon center and thereby forming, regioselectively and through cyclization of the initially formed tosylcarbamate,¹⁷ the anticipated oxazolidinone **21** (61%) that could either be acetylated under standard conditions to give diacetate **22** (98%) or treated with methanolic sodium hydroxide to give triol **23** (90%). The structure of compound **22** was confirmed by single-crystal X-ray analysis (see SI for details).

Scheme 3: A protocol for establishing the aminoconduritol core of *ent*-kirkamide (*ent*-**1**)

The reactions used in the elaboration of compound **23** to the *ent*-kirkamide derivative **3** and its analogue **24** are shown in Scheme 4.

Scheme 4: Conversion of triol **23** into target **3** and analogue **24**

Thus, cyclohexenyl iodide **23** could be converted into the corresponding dimethyl or Weinreb amides **3** (91%) and **24** (87%), respectively, using conditions similar to those employed in the conversion **12** $\rightarrow$ **13**. All of the NMR spectral data obtained on these amide-containing products were entirely consistent with the illustrated structures and that of compound **3** confirmed by single-crystal X-ray analysis.

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