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A Novel Desymmetrization Reaction of an Acetogenin Precursor: A Formal Synthesis of Trilobacin and Asimicin

Zheming Ruan and David R. Mootoo*

Department of Chemistry, Hunter College/CUNY, 695 Park Avenue, New York, NY 10021

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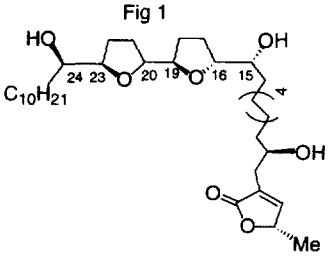
Abstract: A two-directional strategy which is based on the haloetherification reaction of a bis-5,6-O-isopropylidene alkene, is applied to the synthesis of a versatile relay compound for the bis-THF containing acetogenins.

Fig 1

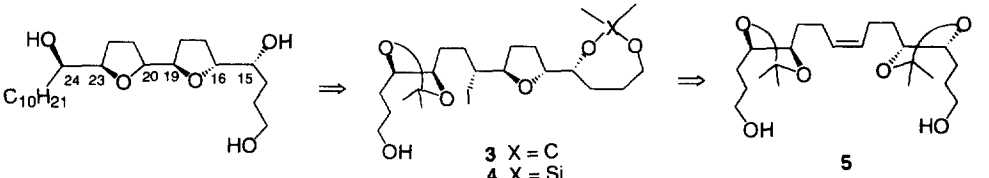


Trilobacin 20S; Asimicin 20 R

The bis-THF containing acetogenins of which asimicin and trilobacin are two examples, have attracted considerable interest because of their potent antitumor activities.[1,2] Several synthetic methodologies have been developed.[3,4] Relay compounds which may be elaborated into diastereomeric bis-THF are of interest because of the existence of a wide range of stereochemical motifs. Strategies in which the core bis-hydroxymethyl-bis-THF residue is related to a C2-symmetric precursor are attractive because of the possibility of assembling such structures in an expedient fashion. However, the main drawback in this approach is the requirement for a desymmetrization step, which is generally not efficient.[4a,f,h,5] In this paper we present a desymmetrization strategy which centers on the synthesis of *trans*-2,5-disubstituted THF's via the iodoetherification reaction of 5,6-O-isopropylidene alkenes.[6]

A two directional version of this strategy relates bis-THF core structures **1** and **2** to a C2-symmetric bis-isopropylidene alkene **5**. Iodocyclization of **5** followed by formation of the acetal or siloxane derivative of the initial iodoetherification product would lead to bis-acetal THF iodides **3** or **4**. Such bis-acetal THF's are potentially very versatile relay compounds for the bis-THF acetogenins. In addition to having their primary alcohols positions distinguishable, the configuration at the iodide carbon may be varied, and the different reactivities of the acetal protecting groups would allow for selective exposure of any one of the the two secondary alcohols for configurational interconversion.

Scheme 1



1 Trilobacin bis-THF Core (20S)
2 Asimicin bis-THF Core (20R)

3 X = C
4 X = Si

Versatile Relay Compound for Synthesis of bis-THF Acetogenins

5

C2 Symmetric Precursor

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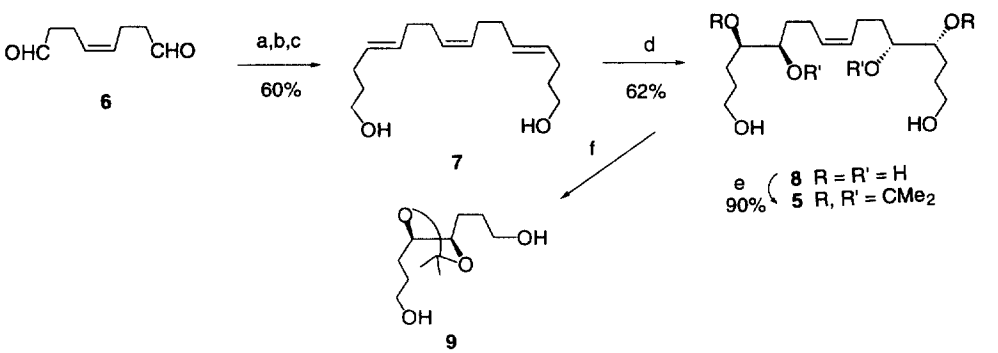
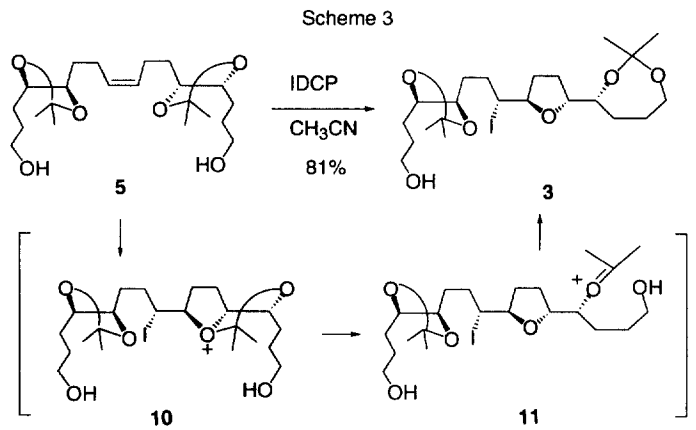
The bis-isopropylidene alkene **5** was prepared from the known dialdehyde **6** which is easily obtained from cyclooctadiene.[7] Addition of vinylmagnesium bromide to **6** provided the bis-allylic alcohol which was subjected to a double Johnson-Claisen rearrangement.[8] DIBALH reduction of the rearranged product gave the E,Z,E-triene diol **7**. Double dihydroxylation of **7** in the presence of AD mix-β gave the hexaol **8** in 62% yield.[9] Acetonation of **8** provided the desired bis-isopropylidene alkene **5**. NMR analysis of **5** and **8** indicated less than 5 % of the corresponding diastereomeric products with respect to the double dihydroxylation reaction, suggesting that this process was highly enantioselective.[10] This was confirmed by conversion of **5** to known diol **9** ($[\alpha]^{26}_{D}$ Found: +29 (c 0.51, $CHCl_3$); Lit.: +29.8 (c 2.00, $CHCl_3$)).[11] The reactions involved in the five step sequence from **6** to **5** were all straightforward and this facilitated preparation of **5** on up to five gram batches.

Scheme 2



(a) Vinylmagnesium bromide, THF; (b) $CH_3C(OEt)_3$, CH_3CH_2COOH, 138-140 °C; (c) DIBALH, CH_2Cl_2, -78°C; (d) AD mix-β; (e) $Me_2C(OMe)_2$, CSA, DMF; (f) (i) O_3,CH_2Cl_2, MeOH then Ph_3P; (ii) $NaBH_4$, EtOH

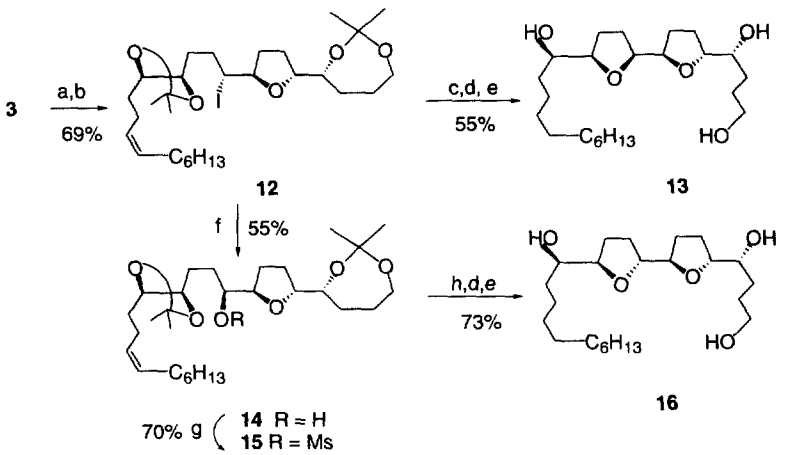
Scheme 3



To our pleasant surprise, treatment of **5** with iodonium dicollidine perchlorate (IDCP) in anhydrous acetonitrile led to the bis-O-isopropylidene THF-iodide **3** in 81% yield.[12] Thus formation of the *trans*-2,5-disubstituted THF and differentiation of the primary alcohols were achieved in a single step. Presumably the formation of the seven membered acetal arises through capture of the intermediate oxocarbenium ion **11** by the proximal primary alcohol. In order to illustrate the synthetic versatility of the cyclization product, **3** was transformed to **13** and **16**, known bis-THF precursors of trilobacin and asimicin.

Swern's oxidation of **3**, followed by Wittig reaction on the resulting aldehyde provided the alkene **12**. Acetal hydrolysis in **12** and treatment of the tetraol product in pyridine at 100 °C resulted in formation of the second THF ring, in 60% yield from **12**. Hydrogenation of the bis-THF product led to **13**. The asimicin subunit was prepared by first conversion of **12** to the mesylate **15**. This was carried out in two steps, iodide displacement to the alcohol **14**, followed by mesylation of the alcohol. Acetal hydrolysis and THF formation was carried out as for the trilobacin system to give the known asimicin core **16** in 82% yield from **15**.[13]

Scheme 4



(a) Swern's Ox.; (b) $C_6H_{13}CH{=}PPh_3$, THF; (c) HCl, H_2SO_4 ; (d) py; 100°C;
(e) H_2 / Pd / C, EtOAc; (f) KO_2, DMF-DMSO; (g) MsCl; py. ; (h) BF_3. Et_2O, MeOH

In summary, the the synthesis of a versatile relay compound for synthesis of bis-THF acetogenins has been developed. A key aspect is the novel example of the iodoetherification reaction for the desymmetrization of a C2 symmetric precursor. The synthesis of known trilobacin and asimicin bis-THF cores **12** and **15** were carried out in three and five steps respectively from a central THF-iodide **3**, which is obtainable in nine steps from cyclooctadiene. Importantly, the use of relatively straightforward and inexpensive reactions allow for large scale preparations. Exploitation of the different reactivity of the two acetals in **3** towards the synthesis of other bis-THF diastereomers are currently underway.

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(9) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. For a related double dihydroxylation, see Hoye, T.R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981-1984. The diol obtained from monodihydroxylation was also obtained as a side product in 20% yield and was resubjected to the reaction conditions to provide additional **8**.

(10) Compound **5**: IR (neat) 3419, 1448 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.58 (m, 12H), 2.14 (m, 4H), 3.58 (m, 8H), 3.82 (bs, 2H, D_2O exchange), 5.35 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 27.3, 27.4, 29.5, 29.5, 32.7, 62.5, 80.4, 80.8, 108.1, 129.3. HRMS calcd for $C_{22}H_{40}O_6$ (M+H) 401.2903, found 401.2903.

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(12) Compound **3:** ^1H NMR (300 MHz, $CDCl_3$) δ 1.31, 1.32 (both s, 6H), 1.36 (s, 6H), 1.65 (m, 12H), 1.95, 2.05 (both m, 4H), 2.40 (bs, 1H), 3.60 (m, 7H), 3.85 (m, 1H), 4.01 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 25.4, 27.5, 28.5, 29.4, 29. 7, 30.6, 31.2, 32.1, 33.0, 41.9, 62.1, 62.8, 74.3, 80.0, 80. 9, 82.6, 82.8, 100.8, 108.5. HRMS calcd for $C_{22}H_{40}O_6I$ (M+H) 527.1870, found 527.1869.

(13) The ^1H and ^{13}C NMR data for **13** and **16** were essentially identical to the spectra provided by Dr.'s Keinan and Sinha (see ref. 4b). Compound **13**: $[\alpha]^{23}_D$ = +1.4 (c 0.38, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, 3H), 1.26 (m, 16H), 1.42 (m, 2H), 1.50 (m, 2H), 1.71 (m, 4H), 1.75 (m 2H), 1.86 (m, 1H), 1.93 (m, 1H), 1.96 (m, 1H), 2.05 (m, 1H), 2.90 (bd, 3H, D_2O exchange), 3.39 (m, 1H), 3.43 (m, 1H), 3.65 (m, 2H), 3.83 (m, 2H), 3.97 (m, 1H), 4.06 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.3, 22.9, 26.0, 26.9, 28.4, 29.0, 29.4, 29.5, 29.8, 29.9, 30.8, 32.1, 34.5, 62.9, 74.0, 74.7, 81.1, 81.8, 82.7, 83.2. HRMS calcd for $C_{23}H_{45}O_5$ (M+H) 401.3267, found 401.3266. Compound **16**: $[\alpha]^{23}_D$ = +9.5 (c 0.40, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$), δ 0.88 (t, 3H), 1.26 (m, 16H), 1.39 (m, 2H), 1.50 (m, 2H), 1.65 (m, 4H), 1.72 (m, 2H), 1.97 (m, 4H), 2.65 (bd, 3H, D_2O exchange), 3.38 (m, 1H), 3.45 (m, 1H), 3.67 (m, 2H), 3.85 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.3, 22.9, 25.9, 28.6, 29.1, 29.5, 29.8, 29.9, 30.7, 32.1, 33.7, 63.1, 74.3 (two carbons), 81.9, 82.0, 83.1, 83.4. HRMS calcd for $C_{23}H_{45}O_5$ (M+H) 401.3267, found 401.3266.