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LETTERS

SYNTHESIS OF THE C(19)-C(32) FRAGMENT OF SCYTOPHYCIN C VIA STEREOSPECIFIC METHYLATION OF γ,δ-EPOXY ACRYLATES WITH TRIMETHYLALUMINUM

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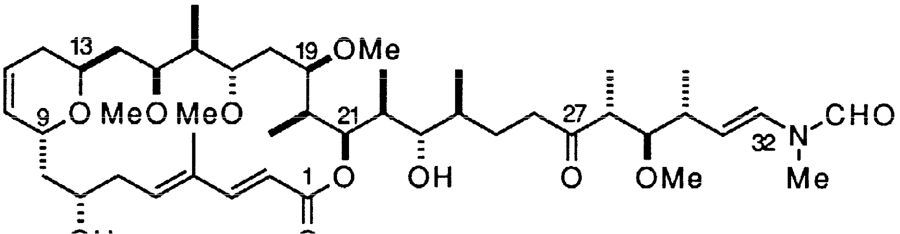
Abstract: The synthesis of the C(19) - C(32) fragment of Scytophycin C is described which features an iterative, stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum and the use of Roush's (*S*,*S*)-diisopropyltartrate-*E*-crotylboronate.

The Scytophycins,[1] which comprise a group of highly functionalized macrolides isolated from the blue-green alga *Scytonema pseudohofmanni*, exhibit potent solid tumor activity *in vitro*,[2] making them exciting candidates for *in vivo* evaluation. Unfortunately, the Scytophycins are rare and have been isolated in only minute quantities. We detail below a stereocontrolled synthesis of the C(19) - C(32) fragment **2**[3] of Scytophycin C(**1**),[4] which features an iterative, stereospecific methylation of γ,δ-epoxy acrylates[5] for elaboration of polypropionate chains.



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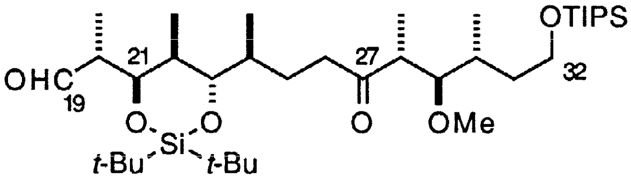

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The synthesis of **2** commences with the known chiral epoxide **3**,[6] prepared previously by Kishi in connection with synthetic studies on Rifamycin S. The C(20) - C(22) anti, syn stereotriad present in **2** was elaborated via the stereospecific methylation of γ,δ-epoxy acrylate **4** employing trimethylaluminum in the presence of water.[5] Toward this end, alcohol **3** was transformed into unsaturated ester **4** via a Swern oxidation [DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C] and an *E*-selective Horner-Wadsworth-Emmons reaction [NaH, THF,

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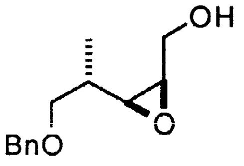
[$(EtO)_2POCH_2CO_2Et$, 0 °C, 15 min; RCHO, -78 °C, 1.5 h] in 92 % overall yield. Treatment of a solution of chiral (*Z*)-epoxy acrylate **4** in 1,2 dichloroethane in the presence of 6.0 equiv of water cooled to -30 °C with 10 equiv of a 2.0 M solution of trimethylaluminum in hexane gave rise to **5**, $[\alpha]_D^{25}$ -6.5 (c 2.71, $CHCl_3$), as the sole product in 95 % yield. Note that the reaction proceeds cleanly and stereospecifically with net inversion of configuration about C(22). The presence of water is critical since in its absence reaction does not proceed to any appreciable extent.



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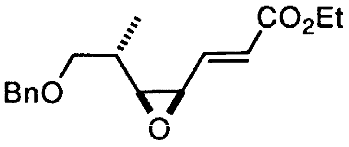

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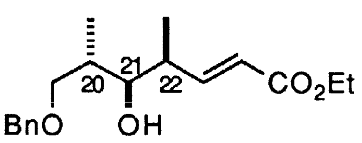

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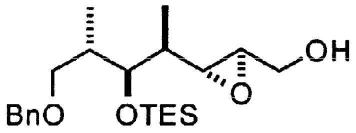
Having established the desired anti, syn arrangement about the C(20)-C(21) and C(21)-C(22) stereocenters in compound **5**, a second iteration of the the above protocol employing γ,δ-epoxy acrylate **7** was anticipated to furnish **8**, via inversion of configuration about C(24). Toward this end, the hydroxyl group in compound **5** was protected (TESCl, DMAP, imidazole, DMF, 40 °C, 2 h) and the ester functionality was reduced [*i*-Bu_2AlH, hexane:CH_2Cl_2 (2:1), -78 °C, 1.5 h] to the corresponding *trans*-allylic alcohol which was epoxidized (MCPBA, CH_2Cl_2, -10 °C, 1 h) giving rise to **6** in 97 % overall yield. The conversion of **6** into **7** was realized (74 % overall yield) in straightforward fashion utilizing a three-step sequence involving sequential Swern oxidation/Horner-Wadsworth-Emmons reaction as detailed above, followed by deprotection (TBAF, THF, 0 °C, 1 h) of the C(23) hydroxyl. Addition of 10 equiv of a 2.0 M solution of Me_3Al in hexane to a solution (cooled to -30 °C) of **7** in 1,2-dichloroethane containing 6.0 equiv of water afforded, after 6 h, an 85 % yield of **8**, $[\alpha]_D^{25}$ + 24.8 (c 0.25, $CHCl_3$), possessing the desired anti, anti arrangement about C(22)-C(23) and C(23)-C(24). The major feature of the above methodology is that methylation occurs stereospecifically. Thus (*E*)-epoxy acrylates provide access to compounds possessing an anti relationship between substituents. In contrast, (*Z*)-epoxy acrylates generate a syn arrangement.



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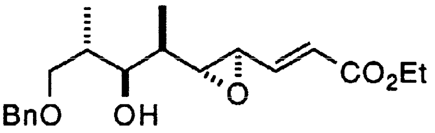

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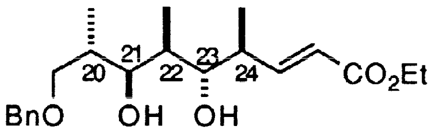

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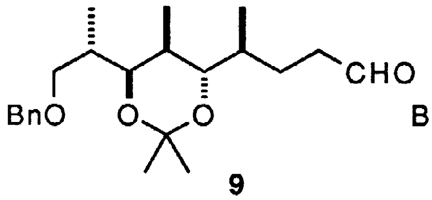
In order to set the stage for elaboration of the remaining stereocenters at C(28)-C(30), substrate **8** was transformed [(a) 2-methoxypropene, PPTS, Et_2O, 1.5 h; (b) H_2, Rh/Al_2O_3, EtOH, 5 h; (c) *i*-Bu_2AlH, pentane, -100 °C, 1 h] into aldehyde **9** in 90 % overall yield. Exposure of **9** to (*S,S*)-diisopropyltartrate-*E*-crotylboronate[7] in toluene at -78 °C afforded **10** in 82 % isolated yield. Protection [KH, 18-c-6, PMBCl, THF, 2 h] of the C(27) hydroxyl as its *p*-methoxybenzyl ether provided, after chromatography on silica gel, not the anticipated product, but instead the corresponding diol derived from cleavage of the acetonide. Since the acetonide in **10** proved to be exceedingly labile, the diol obtained after protection of the C(27) hydroxyl was converted [$(t\text{-}Bu)_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 16 h] into the bis-*t*-butylsilylene derivative **11**, $[\alpha]_D^{25}$ -24.6(c 1.2, $CHCl_3$), in 75 % overall yield.



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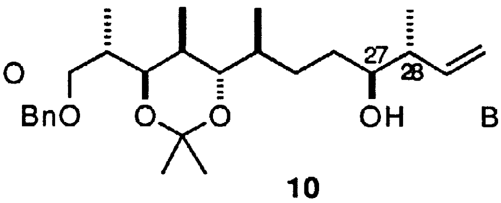

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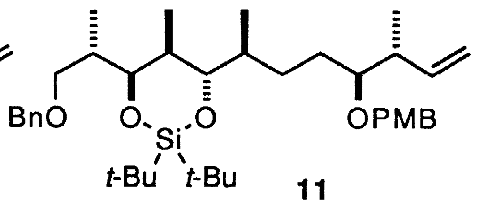
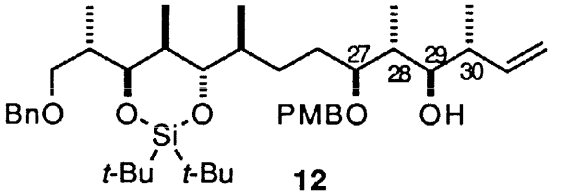


11

With the configuration at C(28) secure (note the configuration at C(27) is of no consequence since it will be eventually oxidized), efforts were focused on elaboration of the remaining two stereocenters, C(29) and C(30) via crotylboronate chemistry. Oxidative cleavage [(a) OsO_4, NMO, H_2O, acetone, *t*-BuOH, 4 h; (b) $Pb(OAc)_4$, benzene, 1 h] of the olefin in **11** generated the corresponding aldehyde which was treated with (*S*,*S*)-diisopropyltartrate-*E*-crotylboronate. Unfortunately, in this mismatched case, the stereoselectivity was less than ideal giving rise (65 % overall) to a 1:1.5 mixture of **12** and **13** which were readily separable by chromatography.



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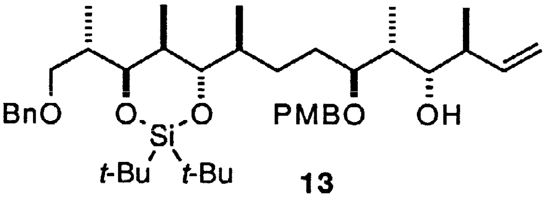

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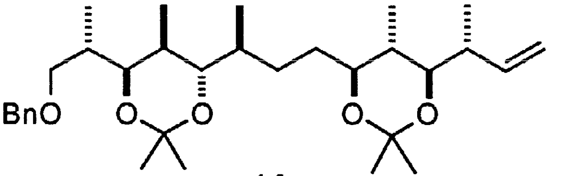
In order to determine which diastereomer was the desired one, **12** and **13** were transformed into the bis-acetonides **14** and **15**, respectively. This was accomplished via a four-step sequence involving protection of the C(29) hydroxyl as its *t*-butyldimethylsilyl ether, removal of the *p*-methoxybenzyl ether, exhaustive desilylation, and acetonide formation. The stereochemical assignments for **14** and **15** follow from their respective ^{13}C NMR spectra



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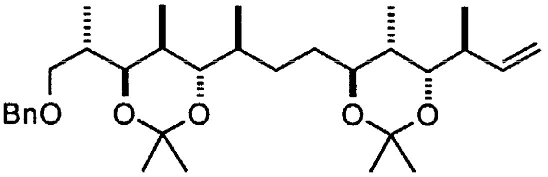

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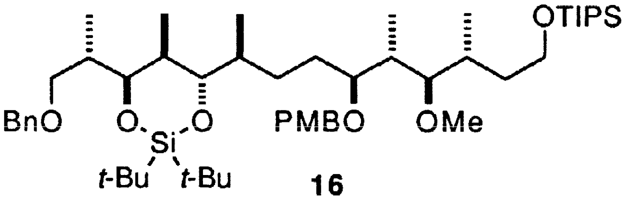
and are based on independent observations by Rychnovsky[8] and Evans[9] concerning the ^{13}C NMR spectra of acetonides derived from syn and anti 1,3-diols. Examination of the ^{13}C NMR spectrum of **15** revealed the presence of two anti acetonides as evidenced by four resonances [23.5, 23.8, 24.9 and 25.4 ppm] and two at 100.3 and 100.7 ppm. Inspection of the ^{13}C NMR spectrum of **14** showed one syn and one anti acetonide as evidenced by one resonance at 19.4 ppm, two at 23.6 and 25.4 ppm, and one at 30.1 ppm. With respect to the two quaternary carbons, one resonance appeared at 97.7 ppm and the other at 100.3 ppm.

Methylation [KH, 18-c-6, MeI, THF, 0 °C, 1 h] of the C(29) hydroxyl in **12** followed by hydroboration [$((C_6H_5)_3P)_3RhCl$, catecholborane, CH_2Cl_2, 15 min][10] gave the corresponding alcohol which was protected[TIPSOTf, 2,6-lutidine, CH_2Cl_2, 2 h] as its triisopropylsilyl ether affording **16**, $[\alpha]_D^{25}$ -33.1(c 0.78,

$CHCl_3$), in 65 % overall yield. Completion of the synthesis of the C(19) - C(32) fragment **2** was accomplished in two steps. Removal [DDQ, CH_2Cl_2, H_2O, 1.5 h] of the two benzyl ethers and subsequent oxidation [Dess-Martin periodinane, CH_2Cl_2, 30 min] provided **2**, $[\alpha]_D^{25}$ -58.1 (c 0.78, $CHCl_3$) [lit.[3] $[\alpha]_D^{25}$ -58.3 (c 1.0, $CHCl_3$), whose spectral properties (^{13}C NMR and ^1H NMR) where identical in all respects with the spectral data provided by Professor Ian Paterson.



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