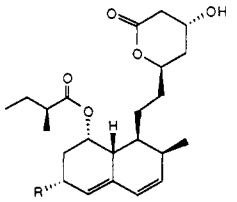
Polyhydroxylated Seven-Membered Chiral Building Blocks. Asymmetric Synthesis of Compactin Analogues

Summary: Enzymatic (electric eel acetylcholinesterase) hydrolysis of meso diacetate **5** provided **6**, which was elaborated into the compactin analogues, (+)- and (−)-**10**.

Sir: Compactin (**1a**) and mevinolin (**1b**) are potent competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme involved in the rate-limiting step of cholesterol biosynthesis in humans.[1] Consequently, considerable attention has been devoted to the synthesis of these hypocholesterolemic agents.[2] We have developed a flexible synthesis of the lactone moiety that can easily give access to analogues, particularly those that are modified in the octalin unit.



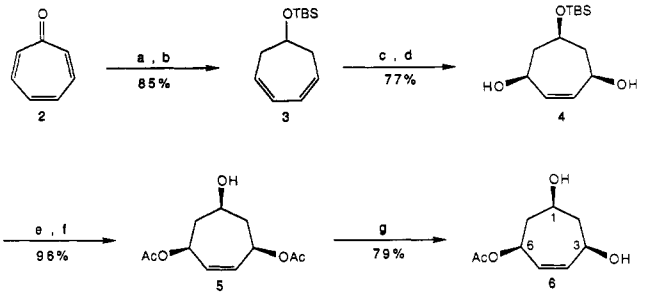
1a = H
1b = Me

The strategy employed in this study focused on the assembly of an appropriately functionalized optically active polyhydroxylated seven-membered ring intermediate (**6**), which could be elaborated into either (−)- or (+)-compactin analogues. The strategic polyhydroxy intermediate **6** was prepared in seven steps and 49% overall yield from tropone (**2**), as outlined in Scheme I.

Upon treatment with $NaBH_4$ in aqueous MeOH, **2** underwent 1,8-hydride reduction;[3] the product was converted to the *tert*-butyldimethylsilyl (TBS) ether **3**. Treatment of silyl ether **3** with singlet oxygen afforded a 5:1 (syn/anti) mixture of endo peroxides.[4] The major isomer was separated by chromatography (silca gel, 1:10 ether/petroleum ether) and reduced with Zn/AcOH[5] or SmI_2 to obtain diol **4** in 77% yield. Meso diacetate **5** was acquired by a two-step sequence involving diol protection as the diacetate followed by silyl ether deprotection.

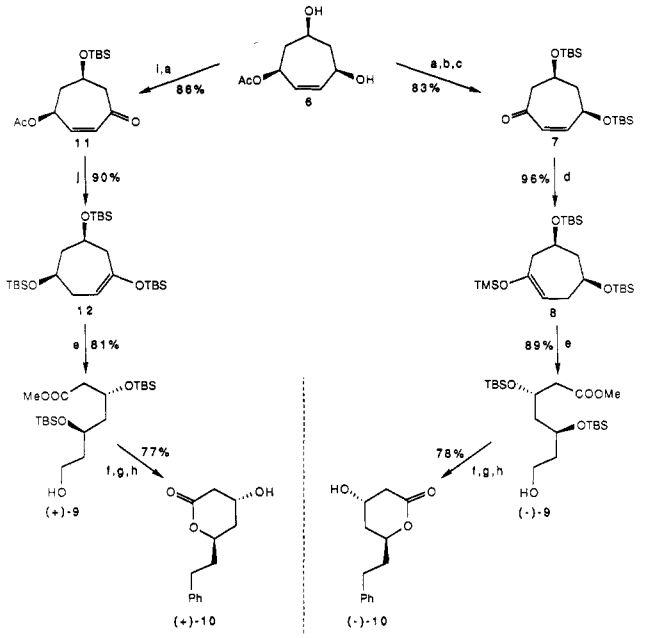
Stimulated by earlier success of enzymatic enantiotopic differentiation of meso diacetoxycyclopentane derivatives,[6] we treated **5** in an aqueous suspension with electric eel acetylcholinesterase[7] (1 mg of enzyme[8]/1 g of **5**); 6(*S*)-acetoxy-4-cycloheptene-1(*S*),3(*R*)-diol (**6**),[9] $[\alpha]^{25}_D$ +11.44° (*c* 1.18, $CHCl_3$), was obtained in 79% yield.

Scheme I[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, H_2O; (b) *tert*-butyldimethylsilyl chloride, imidazole, DMF; (c) O_2, *hν*, *meso*-tetraphenylporphine, MeOH, CH_2Cl_2; (d) Zn, AcOH, or SmI_2, THF; (e) Ac_2O, Et_3N, cat. DMAP; (f) HF, CH_3CN, Py; (g) electric eel acetylcholinesterase, aqueous phosphate pH 6.9 buffer, 25 °C.

Scheme II[a]



[a] Reaction and conditions: (a) TBSOTf, lutidine, CH_2Cl_2, 0 °C; (b) KOH, MeOH, 0 °C; (c) PDC, CH_2Cl_2; (d) cat. MeCu, DIBAL-HMPA, −50 °C, then at −78 °C, MeLi, TMSCl; (e) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_4$ followed by CH_2N_2; (f) TsCl, Et_3N, DMAP; (g) Ph_2CuLi, Et_2O, 0 °C; (h) HF, CH_3CN; (i) MnO_2, CH_2Cl_2; (j) cat. MeCu, 2.5 equiv of DIBAL in HMPA/THF, −50 °C, then at −78 °C, MeLi (2.5 equiv), TBSOTf (2.5 equiv).

The stage was now set to complete the synthesis of the compactin analogues (−)-**10** and (+)-**10** as shown in Scheme II. Key compound **6** was converted to enone **7**, $[\alpha]^{25}_D$ +32.56° (*c* 1.81, $CHCl_3$), in 83% overall yield by protecting group manipulation followed by PDC oxidation. The assembly of the desired silyl enol ether **8** was accomplished

(1) The pharmacology and mechanism of action for these agents has been reviewed (Endo, A. *J. Med. Chem.* **1985**, *28*, 401). Vega, L.; Crundy, S. *J. Am. Med. Assoc.* **1987**, *257* (1), 33 and references therein).

(2) For recent reviews, see: Rosen, T.; Heathcock, C. A. *Tetrahedron* **1986**, *42*, 4909. Roark, W. H.; Roth, B. D. *Tetrahedron Lett.* **1988**, *29*, 1255 and references therein.

(3) Schuster, D. I.; Palmer, J. M.; Dickerman, S. C. *J. Org. Chem.* **1966**, *31*, 4281.

(4) Floyd, D. M.; Cimarusti, C. M. *Tetrahedron Lett.* **1979**, *20*, 4129.

(5) Schreiber, S. L.; Goulet, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 8120.

(6) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, *108*, 5655; **1988**, *110*, 4727 and references therein.

(7) For enzymatic hydrolyses related to this work, see: Deardorff, D. R.; Mathews, A. J.; McMeekin, D. S.; Craney, C. L. *Tetrahedron Lett.* **1986**, *27*, 1255; Pearson, A. J.; Harjinder, S. B.; Lai, Y. S. *J. Chem. Soc., Chem. Commun.* **1987**, 519. Pearson, A. J.; Lia, Y. S. *J. Chem. Soc., Chem. Commun.* **1988**, 442.

(8) Obtained from Sigma Chemical Co. (Cat. No. C-3389).

(9) The ^1H NMR spectrum of **6** recorded in the presence of the chiral lanthanide shift reagent Eu(hfbc)$_3$ indicated high optical purity. Compound **6** gave a single peak in HPLC with the use of a chiral column (Chiral Pak OT(+), Japan Spectroscopic Co., Ltd.). The absolute stereochemistry 1*S*, 3*R*, 6*S* (as shown in Scheme I) and enantiomeric excess (ee >95%) of compound **6** were assigned by conversion to unnatural compactin analogue (−)-**10** (ref 10).

(10) (a) Bonini, C.; Mecozzi, S.; Gubbiotti, A.; Fabio, R.; Bonadies, F. *Tetrahedron Lett.* **1987**, *28*, 703. (b) Majewski, M.; Clive, D. L. J.; Anderson, P. C. *Tetrahedron Lett.* **1984**, *25*, 2101.

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with MeCu-catalyzed hydroalumination with DIBAL in HMPA/THF followed by trapping the aluminate with chlorotrimethylsilane.[11] Without purification, this labile substance was ozonized[12] and the crude product was treated with sodium borohydride followed by diazomethane to give hydroxy ester **9**, $[\alpha]^{25}_D$ -7.69° (*c* 0.52, $CHCl_3$), in 87% yield. Tosylation of the hydroxy ester **9** followed by exposure to lithium diphenylcuprate[13] gave the corresponding 7-phenylheptanoate. Acidic (HF, CH_3CN) removal of the silyl ether protecting groups resulted in concomitant lactonization to compound (-)-**10**, $[\alpha]^{25}_D$ -45.20° (*c* 0.44, $CHCl_3$) (lit.[10b] $[\alpha]^{20}_D$ +45.6°).

The preparation of lactone (+)-**10** (natural compactin analogue) was performed along similar lines (Scheme II). Compound **6** was transformed into enone **11**, $[\alpha]^{24}_D$ -19.63° (*c* 1.24, $CHCl_3$), in 86% yield via chemoselective oxidation with MnO_2 followed by hydroxy protection as the silyl ether. Treatment of **11** with catalytic MeCu and 2.5 equiv of DIBAL in HMPA/THF followed by MeLi afforded a bisaluminate species, which was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) to give **12** in 90% yield.[14] Silyl enol **12** was converted to natural compactin analogue (+)-**10** in a series of routine manipulations as described in Scheme II. The optical rotation of (+)-**10** was found to be $[\alpha]^{25}_D$ +46.11° (*c* 0.36, $CHCl_3$) (lit.[10a] $[\alpha]^{25}_D$ +48.80° (*c* 0.20, $CHCl_3$)).

We anticipate that the optically active synthon **6** will be applicable to the synthesis of a number of biologically interesting substrates; studies along these lines are continuing in our laboratory.

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Supplementary Material Available: Spectral data for compounds **3-12** (8 pages). Ordering information is given on any current masthead page.

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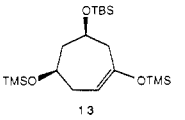
(11) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439.
(12) Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315. White, J. D.; Fukuyama, Z. Y. *J. Am. Chem. Soc.* **1979**, *101*, 226.
(13) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.
(14) Attempts to prepare compound **13** were successful but ozonation resulted in low yields of the desired product.

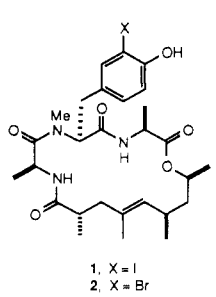


13

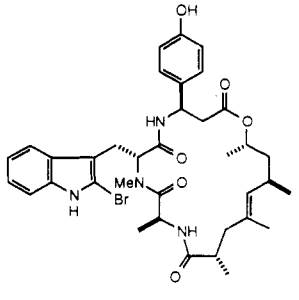
Total Synthesis of Geodiamolide A, a Novel Cyclodepsipeptide of Marine Origin

Summary: Geodiamolide A (**1**), a cyclodepsipeptide isolated from the sponge *Geodia* containing the new amino acid (*R*)-3-iodo-*N*-methyltyrosine, was synthesized from its constituent tripeptide and 8-hydroxynonenoic acid subunits. Final closure of the 18-membered ring was effected via macrolactonization employing dicyclohexylcarbodiimide.

Sir: Geodiamolide A (**1**) and B (**2**),[1] along with jasplakinolide (**3**),[2] are novel cyclodepsipeptides isolated by acetone extraction of the sponges *Geodia* and *Jaspis* sp., respectively. Each of these 18-membered cyclodepsipeptides consists of an 11-carbon, propionate-derived hydroxy acid [(2*S*,6*R*,8*S*)-8-hydroxy-2,4,6-trimethyl-4(*E*)-nonenoic acid] linked to a tripeptide containing a unique amino acid. The pharmacological properties of these substances, especially the potent insecticidal and anthelmintic activity of **3**,[2] have attracted attention, and, recently, the syntheses of both **2** and **3** have been reported by Grieco et al.[3,4] Herein we describe the total synthesis of **1** containing the previously unknown amino acid 3-iodo-*N*-methyl-D-tyrosine. The steric demand imposed by the iodo substituent in this subunit compelled us to adopt a sequence significantly different from that employed for the corresponding tripeptide segment of **2**.[4] Also, in contrast to the previous syntheses of **2** and **3**, our route to the nonenoic acid component of **1** takes advantage of the Claisen rearrangement of an orthopropionate, and thereby establishes the desired substitution at C-2 without the need for a separate methylation.[2,5]

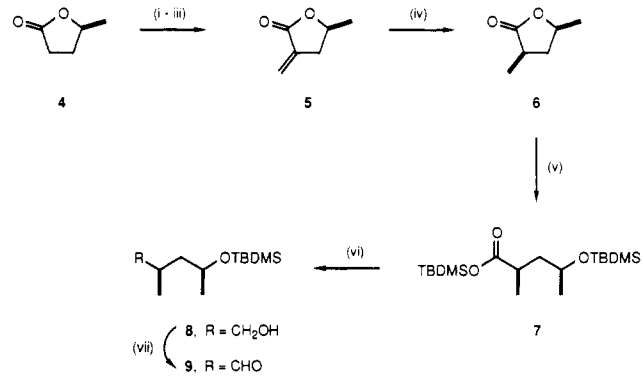


1, X = I
2, X = Br



3

Scheme I[a]



[a] Reagents: (i) HCO_2Me, NaH, Et_2O, 25 °C (93%); (ii) Me_2NH, $NaBH_3CN$, MeOH-HCl, 25 °C (66%); (iii) MeI, MeOH, then 5% $NaHCO_3$, 25 °C (80%); (iv) H_2, 10% Pd/C, EtOH, 25 °C (72%); (v) 2.5 M KOH, THF, 25 °C, then $tBuMe_2SiCl$, imidazole, DMF, 25 °C (70%); (vi) $(iBu)_2AlH$, Et_2O, 25 °C (78%); (vii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C → 25 °C (75%).

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(2) (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797. (b) Zabriskie, T. M.; Klocke, J. A.; Ireland, C. M.; Marcus, A. H.; Molinski, T. F.; Faulkner, D. J.; Xu, C.; Clardy, J. D. *J. Am. Chem. Soc.* **1986**, *108*, 3123.
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