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ENANTIOSELECTIVE SYNTHESIS OF THE ALLEGED STRUCTURE OF NORPECTINATONE[1]

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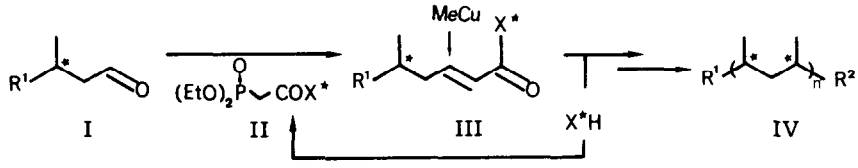
Abstract: The deoxypolypropionate 13 was synthesized from (S)-2-methyl-1-butanol by a reaction sequence featuring two highly π-face selective organocopper/enoate additions 1 → 4 and 7 → 8. Neither 13 (the configuration of which was confirmed by X-ray analysis of 8) nor epimer 16 (prepared via the key step 14 → 15) are identical with norpectinatone.

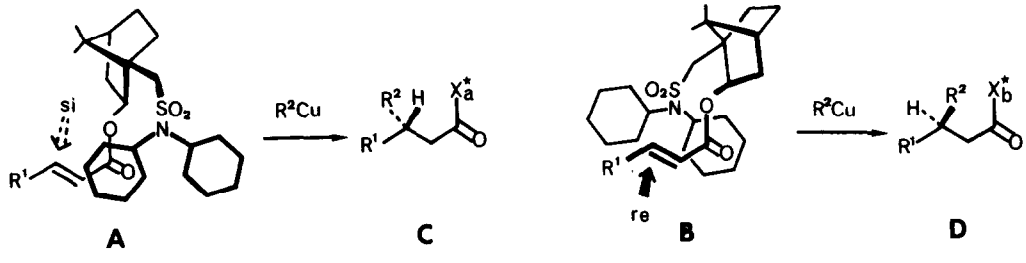
Deoxypolypropionate derivatives IV which feature a saturated aliphatic chain with a sequence of 1,3-disposed methyl groups have been isolated from various sources such as preen glands of water fowl[2], tubercle bacilli[3], marine molluscs[4] and acrid mites[5].

Scheme 1



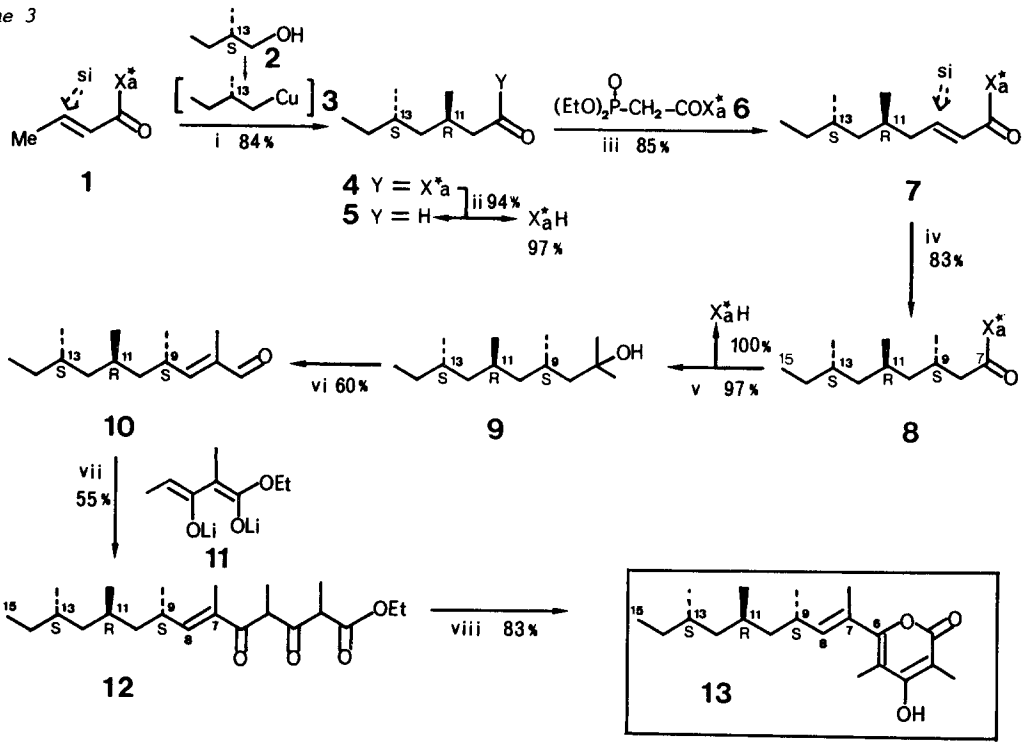
We report here a flexible and predictable synthetic approach to this widespread but so far relatively unaccessible class of natural products. In order to generate each methyl-substituted center with the desired absolute (and relative) topicity we envisaged the combination of Horner-Wittig-(I + II → III) and 1,4-addition- (III → IV) reactions (*Scheme 1*). This strategy relies on the high topological bias provided by the antipodal auxiliary groups X_a* (A → C) or X_b* (B → D)[6] (*Scheme 2*).

Scheme 2



In the following we describe, as a specific example, the stereocontrolled synthesis of enantiomerically pure structure 13 (and of its C(9)-epimer 16) which had been assigned to the pulmonate metabolite norpectinatone [4c] (*Scheme 3*).

Scheme 3



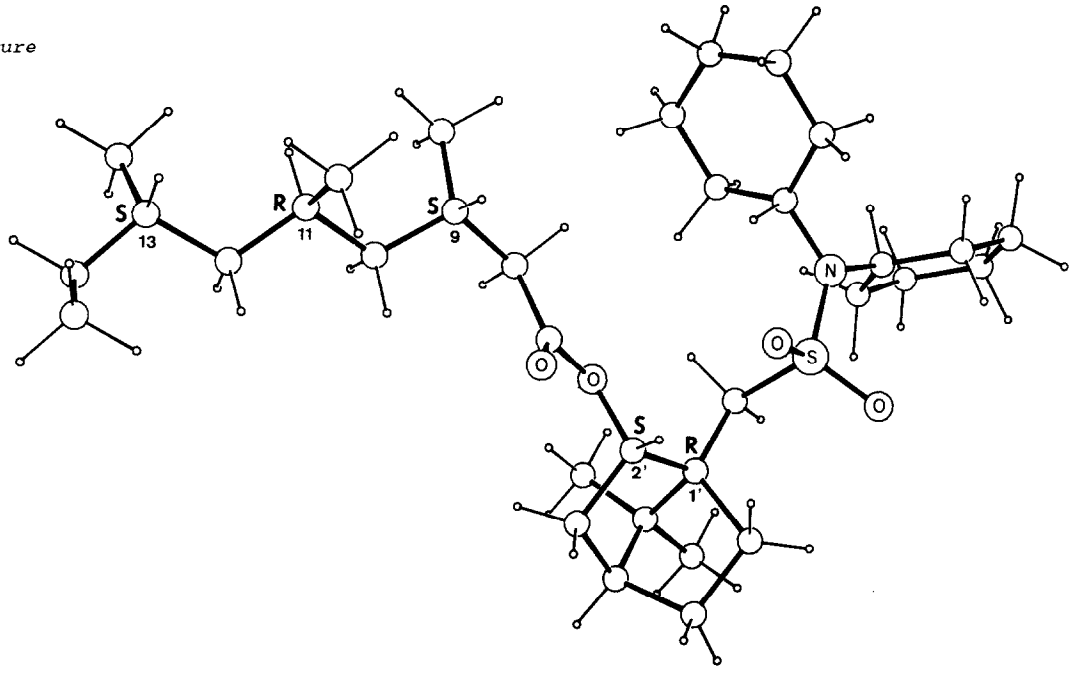
i:1)2, PBr_3,rt, 16h;2) Li(2%Na), Et_2O, 0° →rt, vibromix; 3)$nBu_3P.CuI$, Et_2O, -78° → -20° → -78°, $BF_3.OEt_2$; 4)1 (0.66eq, prepared from X_a*H /crotonoyl chloride/AgCN[7]) -78° → rt. ii: 1) 2.5N NaOH, aq EtOH reflux, extraction (Et_2O), cryst. of X_a*H; 2) $LiAlH_4$, Et_2O, 0° → rt; 3) $(COCl)_2$, DMSO, CH_2Cl_2. iii: LiCl, DBU, CH_3CN, 6 (prepared *via* 1)X_a*H/$BrCH_2COBr$/AgCN;2)$P(OEt)_3$ reflux). iv: 1) $nBu_3P.CuI$, toluene/Et_2O, MeLi, -78° → -30° → -78°, $BF_3.OEt_2$; 2) 7, -35°, 16h. v: MeLi (2.2eq), Et_2O, rt, vi: 1) *p*TsOH, I_2-cat., toluene, reflux; 2) SeO_2 (3eq), EtOH/H_2O-95/5, reflux 16 h.[8] vii 1) LDA (3eq), EtCOCHMeCOOEt (1.5eq), THF, 0°; 2) 10, 0° → rt; 3) $(COCl)_2$, DMSO, CH_2Cl_2. viii: DBU (1.2eq), toluene reflux, 2h.

Starting from the crystalline crotonate 1[9](m.p. 134-5°), addition of copper reagent 3(1.5eq), prepared *in situ* from the (S)-alcohol 2 (Fluka), in Et_2O at -78° to rt gave ester 4[9] (≈100% yield, 97.5% d.e.[10]) which crystallized readily from hexane (m.p. 91-2°, 84% yield, 98.4% d.e.[10]). Ester 4 afforded cleanly aldehyde 5[9] (94% overall) by alkaline hydrolysis (extraction and crystallization of recovered auxiliary alcohol X_a*H, 97%), reduction of the free carboxylic acid with $LiAlH_4$ and *Swern* oxidation[11] of the resulting primary alcohol.

Phosphonate 6[9], required for the *trans*-olefination of 5, was efficiently prepared by acylation of X_a*H with bromoacetyl bromide/AgCN[7] and heating of the bromoester with triethylphosphite. *Horner-Wittig* coupling of 5 and 6 employing *Masamune's* reaction conditions[12] afforded pure (E)-enoate 7[9] (after crystallization of the crude 97:3-E/Z-mixture from hexane, m.p. 120-2°, 85%).

Now the stage was set for the generation of the third asymmetric center C(9). Treatment of enoate 7 with MeLi/CuI.PBu_3/BF_3 (1:1:1, 10eq) at -78° to -35° furnished ester 8[9](crude, 94% d.e.[10]) which was crystallized from hexane (m.p. 106-9°, 83% yield, 96.7% d.e.[10]). The expected (9S,11R,13S) configuration of 8 was confirmed by an X-ray-diffraction analysis[13] as depicted in the *Figure*.

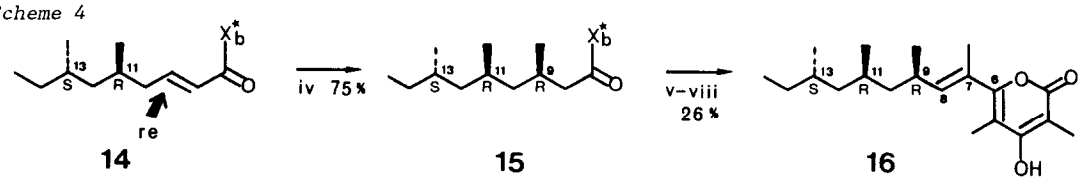
Figure



Accordingly the C(7) to C(15)-chain of the target molecule 13 has been assembled in a highly stereocontrolled manner by means of two *Cβ-Si* face selective enoate additions. It remained to introduce one methyl, the pyrone ring and the (E)-C(7)/C(8)-olefinic bond. To that end the ester 8 was cleaved with MeLi (2.2 eq) to give after chromatography recovered auxiliary X_a*H (100%) and carbinol 9[9](97%). TsOH/I_2-catalyzed dehydration of 9 afforded a 9:1-mixture of trisubstituted/terminal olefins which on allylic oxidation with SeO_2 furnished pure (E)-conjugated aldehyde 10[9] (60% from 9). Aldol-type addition of bislithiated ethyl β-ketoester 11 to aldehyde 10 followed by *Swern* oxidation of the unstable aldol gave diketo-ester 12[9] (55% from 10). Finally, 12 cyclized smoothly on heating with diazabicycloundecene to provide the target molecule 13[9] (83%, solid melting at 101-6°). In comparison with norpectinatone (oil!) of natural origin, 13 showed similar UV-maxima but different chiroptic properties, ^{1}-H-NMR data[9] and notably, ^{13}C-NMR signals at δ=30.5(*d*) and 20.3(*q*)ppm which deviate from those (δ=29.2 and 21.1ppm) of the natural product. We therefore conclude that norpectinatone differs from structure 13 with respect to its side-chain configuration.

To study the possible identity of norpectinatone with structure 16 (or its antipode) we exploited the *Cβ-Re* -face directing capacity of auxiliary group X_b* (*Scheme 4*).

Scheme 4



Analogous methylcopper addition to enoate 14 gave the (9R,11R,13S) isomer 15[9] in 92.4% d.e.[10] which was raised to 95% d.e.[10] (75% yield) by crystallization. Following the above procedure 15 was converted to 16[9] which exhibits a similar ^{13}C-NMR spectrum as norpectinatone

but differs with regard to its chiroptic and ^{1}H-NMR properties. Consequently, neither structure 16 nor its enantiomer correspond to the natural product. Of more general interest is the finding that the topicities of the additions 7 → 8 and 14 → 15 are opposite but almost equally efficient.

Accordingly, during formation of center C(9) the auxiliary-derived π-facial bias overrides that of the preexisting centers C(11) and C(13). This underscores the applicability of the above approach to stereorational syntheses of various, topologically different, deoxypolypropionates.

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REFERENCES AND NOTES

1 Presented at the XI Conference on Isoprenoids, Jachranka/Poland, Sept. 1985 and at the Autumn Meeting of the Swiss Chemical Society, Bern, Oct. 1985, Abstr. OVI-3,p.9.

2 G. Odham, E. Stenhagen, *Acc. Chem. Res.* 1971, *4*, 121.

3 M.A. Spielmann, R.J. Anderson, *J. Biol. Chem.* 1936, *112*, 759; J. Cason, G. Sumrell, *ibid.* 1951, *192*, 405; C.F. Allen, J. Cason, *ibid.*, 1956, *220*, 407: N. Polgar, R. Robinson, *Chem. Ind. (London)* 1956, *220*, 407; C. Asselineau, J. Asselineau, R. Ryhage, S. Ställberg-Stenhagen, E. Stenhagen, *Acta Chem. Scand.* 1959, *13*, 822.

4 a) J.E. Hochlowski, D.J. Faulkner, *Tetrahedron Lett.* 1983, *24*, 1917; b) J.E. Biskupiak, C.M. Ireland, *ibid.* 1983, *24*, 3055; c) R.J. Capon, D.J. Faulkner, *J. Org. Chem.* 1984, *49*, 2506.

5 Y. Kuwahara, L.T.M. Yen. Y. Tominaga, K. Matsumoto, Y. Wada, *Agric. Biol. Chem.* 1982, *46*, 2283.

6 W. Oppolzer, P. Dudfield, T. Stevenson, T. Godel, *Helv. Chim. Acta* 1985, *68*, 212.

7 S. Takimoto, J. Inanaga, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* 1976, *49*, 2335.

8 U.T. Bhalerao, H. Rapoport, *J. Am. Chem. Soc.* 1971, *93*, 5311.

9 All new compounds were characterized by IR, ^{1}-H-NMR (360 MHz) and MS. Observed $[\alpha]_D$ - values (T=19 to 21°C, $CHCl_3$, c=g/100ml): 1: +39.5° (1.54); 4: +36.6° (1.3); 7: +44.9° (1.55); 8: +30.0° (1.52); 10: +46.6° (2.0); 13: +71.3° (1.08);16: -60.0° (2.04); norpectinatone, lit.[4c]: +49.2° (2.5). 13 exhibits a ^{1}-NMR- triplet (J=7.5 Hz, 3H) at δ=0.90 ppm, 16 displays this triplet at δ=0.87 ppm, wheras norpectinatone is reported[4c] to show this triplet at δ=0.81 ppm. UV(EtOH) of 13: λ_{max} at 300 nm(ϵ=10450); 231.9(ϵ=1940).

10 The indicated diastereomeric excesses d.e. of esters 4, 8, and 15 were determined by saponification, followed by preparation and HPLC analyses of their (S)-α-naphthylethylamides: see ref.[6] and W.H. Pirkle, J.R. Hauske, *J. Org. Chem.* 1977, *42*, 1839.

11 A.J. Mancuso, S.L. Huang, D. Swern, *J. Org. Chem.* 1978, *43*, 2480

12 M.A. Blanchette, W. Choy, Y.T. Davis, A.P. Essenfeld, S. Masamune, W.R. Roush, T. Sakai, *Tetrahedron Lett.* 1984, *25*, 2183.

13 Crystallographic data have been deposited at the *Cambridge Crystallographic Data Center*. Observed and calculated structure factors may be obtained from one of the authors (*G.B.*) upon request. The crystals (from ethanol) are orthorhombic, a=8.795 (13), b=14.936 (2), c=26.499 (3)Å, space group $P2_12_12_1$, z=4, d_c = 1.106 g.cm^{-3}. The data were collected on a *Philips PW 1100* diffractometer (Mo$K\alpha$). The structure was solved by a direct method (Multan-80) and refined by a full matrix least-squares analysis. The final R-factor based on 1904 observed reflections was 0.073. The positions of the hydrogen atoms were calculated.

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