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TOTAL SYNTHESIS OF NATURAL PRODUCTS HAVING 1,3-SYN-POLYOL, δ-LACTONE OF (2Z,5S,7S,9R,11R)-TETRAHYDROXYHEXACOS-2-ENOIC ACID AND 4,6,8,10,12,14,16,18,20-ALL-SYN-NONAMETHOXY-1-PENTACOSENE

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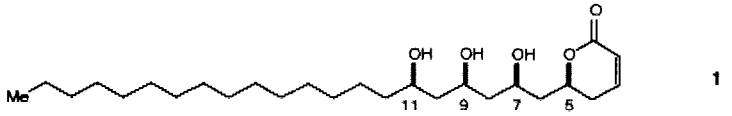
Abstract: First total synthesis of natural products having 1,3-syn-polyol, 1 and 2, has been achieved stereoselectively.

In the precedent paper,[1] we reported an effective and stereoselective method for the convergent synthesis of the extended 1,3-polyol chain. We now report the first total synthesis of natural products having 1,3-all-syn-polyol, δ-lactone of (2Z,5S,7S,9R,11R)-tetrahydroxyhexacos-2-enoic acid (1)[2] and 4,6,8,10,12,14,16,18,20-all-syn-nonamethoxy-1-pentacosene (2)[3] using the present strategy effectively.



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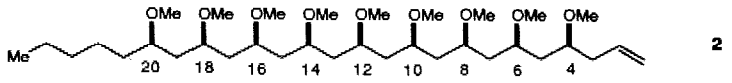
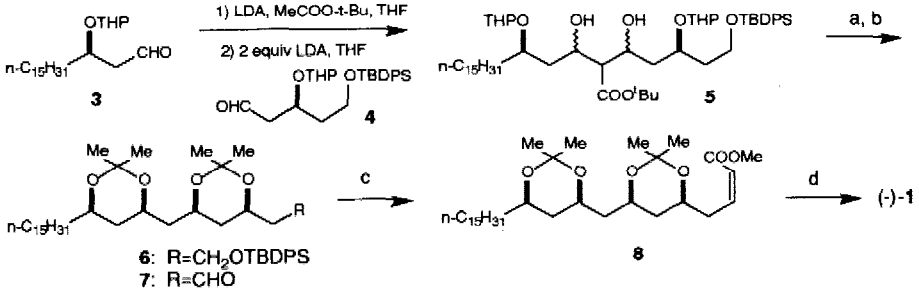


2

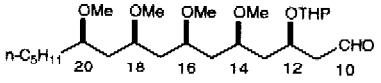
The lactone 1 was isolated from Eupatorium pilosum by Herz[2] and although the absolute as well as relative stereostructure has been determined recently as shown in 1 in this laboratory,[4] total synthesis of 1 itself has not been achieved yet. Aldehyde 3,[5] prepared from (-)-malic acid, was treated with lithium enolate of t-butyl acetate



a) aq AcOH; $Me_2C(OMe)_2$/TsOH/CH_2Cl_2; DIBAH; PhSeCN/Ph_3P; $NaIO_4$; Et_3N/PhH/reflux (72%, 6 steps); O_3/EtOH-AcOEt; K_2CO_3/MeOH-Ether (50%, 2 steps); DIBAH; NaH/CS_2/MeI/THF; n-Bu_3SnH/AIBN/PhMe (91%, 3 steps), b) n-Bu_4NF; $(COCl)_2$/DMSO/CH_2Cl_2, c) $(CF_3CH_2O)_2POCH_2COOMe$/KN$(TMS)_2$/18-Crown-6/THF, d) TsOH/MeOH; TsOH/PhMe

producing a mixture of aldols (87%) which after treatment with 2 equiv LDA was coupled with aldehyde **4** to give diol **5** as a mixture of stereoisomers (49%, 66% based on the consumed aldols). Diol **5** was converted into the pure 5,7,9,11-all-syn-diacetonide **6**[6] stereoselectively in the same way (11 steps) as described in the precedent paper.[1] Treatment of **6** with n-Bu_4NF followed by Swern oxidation produced aldehyde **7** (95%), which was converted into (Z)-α,β-unsaturated ester **8** (77%) as the main product.[7] After deprotection of **8** with CSA in MeOH, lactonization was effected by replacing MeOH with toluene giving (-)-lactone **1**,[8] mp 101°C, $[\alpha]_D^{26}$ -35.7° (c 0.35, MeOH), in 70% yield.[9] 270 MHz ^{1}H-NMR spectra and mp of the synthetic **1** were identical with those of natural **1**.

A mixture of three isotactic polymethoxy-1-alkenes has been isolated from the blue-green alga Tolypothrix conglutinata var. chlorata by Moore.[3] The major component in this mixture has been assigned to have (4S*,6S*,8S*,10S*,12R*,14R*,16R*,18R*,20R*)-nonamethoxy-1-pentacosene (**2**) structure from NMR (100 MHz) data. Total synthesis of the compound having the absolute structure **2** was successfully achieved based on the present convergent method using two aldehyde **9** and **10** as the left and right segments, respectively.



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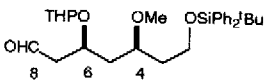
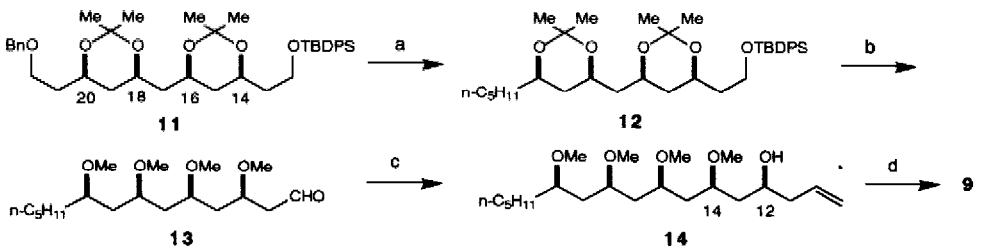


10

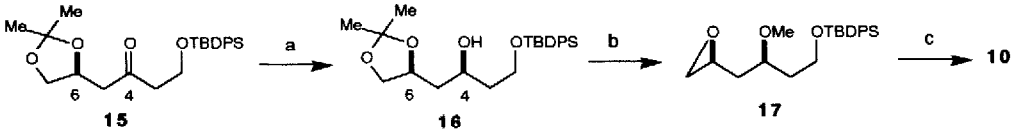
(+)-14,16,18,20-All-syn-tetraol derivative **11**[1,6] was converted into acetonide **12** in 4 steps; 1) debenzylation with Raney Ni (73%), 2) Swern oxidation (99%), 3) Wittig reaction (95%), 4) hydrogenation on Pd-C (91%). Deprotection of acetonide **12** and the subsequent methylation gave tetramethoxyl compound (84%) which on desilylation followed by Swern oxidation produced aldehyde **13** in 90% yield. 12-Hydroxyl group was introduced using (-)-B-allyldiisopinocampheylborane.[10] Although the unexpected 12,14-anti-isomer was obtained in slight excess when ether was used as a solvent,[11] the reaction in toluene produced the desired 12,14-syn-alcohol **14** with high selectivity (15 : 1, 99%).[12] Protection of the hydroxyl group of **14** as THP ether (95%) followed by oxidation with OsO_4-$NaIO_4$ gave aldehyde **9** in 71% yield.



11 **12** **13** **14**

a) Raney Ni/EtOH/reflux; $(COCl)_2$/DMSO/CH_2Cl_2/-78°C/Et_3N; $Ph_3P^+C_3H_7Br^-$/n-BuLi/THF/-78~0°C; H_2/10% Pd-C/EtOH, b) aq AcOH; MeI/KH/THF; n-Bu_4NF/THF; $(COCl)_2$/DMSO/CH_2Cl_2/-78°C/Et_3N, c) (-)-$Ipc_2BCH_2CH{=}CH_2$/PhMe/-78°C, d) DHP/CSA/CH_2Cl_2; OsO_4/$NaIO_4$/aq THF

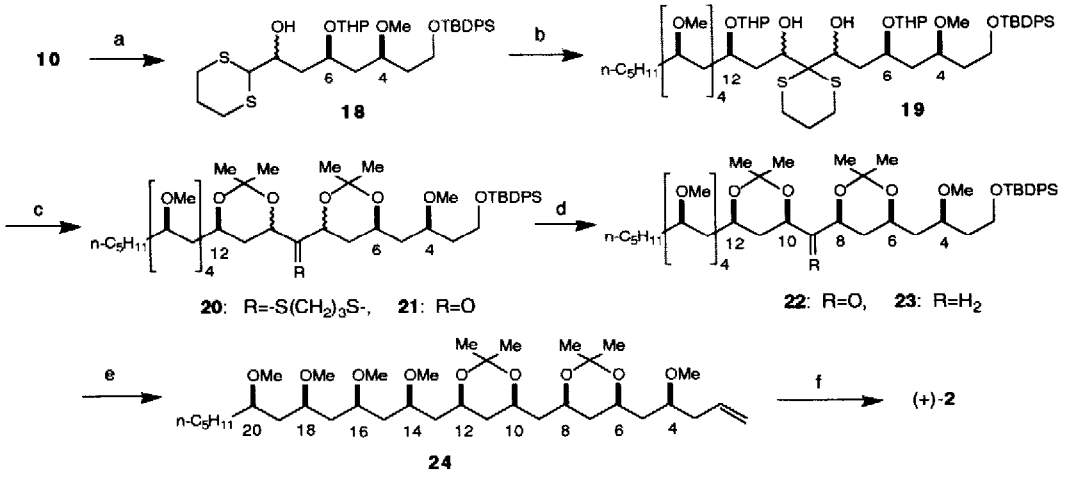
$Zn(BH_4)_2$ reduction[13] of ketone **15**,[14] prepared from (-)-malic acid, afforded 6,8-syn-alcohol **16** with 15.4 : 1 ratio (100%) in toluene.[15,16] The alcohol **16** was converted into aldehyde **10** via epoxide **17** in the conventional way: 1) methylation, 2) deacetonization (87%, 2 steps), 3) tosylation (57%), 4) formation of epoxide (92%), 5) addition of 1,3-dithiane (88%), 6) THP protection (97%), 7) deprotection of thioacetal (67%).



15 **16** **17**

a) $Zn(BH_4)_2$/PhMe/0°C, b) MeI/KH/THF; aq AcOH; TsCl/Py/CH_2Cl_2; K_2CO_3/MeOH, c) n-BuLi/1,3-dithiane/THF/0°C; DHP/CSA/CH_2Cl_2; HgO/$HgCl_2$/aq Acetone/reflux

Addition of lithiated 1,3-dithiane to aldehyde **10** gave alcohol **18** (92%) which was treated with 2 equiv n-BuLi and then aldehyde **9** to give diol **19** (47%). Removal of THP group and treatment with CSA and dimethoxypropane afforded diacetonide **20** (65%). Deprotection of thioacetal **20** with NBS produced a mixture of four isomeric ketones **21**, which was treated with K_2CO_3 in MeOH producing ketone **22** (64%, 2 steps) stereoselectively. The relative configurations at C-6,8,10,12-positions could be determined easily from the coupling constants of C-8 and C-10 protons; signals of both protons appeared completely overlapped at δ 4.72 (dd, J=12.0, 2.4 Hz). Carbonyl group in **22** was removed by 1) DIBAH reduction (90%), 2) xantate formation (100%), and 3) n-Bu_3SnH reduction (99%) giving **23**. The vinyl group was introduced into C-2 position producing **24** by 1) deprotection of silyl group (95%), 2) Swern oxidation (95%), and 3) Wittig reaction (82%). Finally, **24** was, after deacetonization, methylated with KH and MeI to give



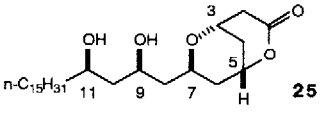
a) n-BuLi/1,3-dithiane/THF/-78°C, b) 2 equiv n-BuLi/HMPA/THF/-78°C/aldehyde **9**, c) aq AcOH; $Me_2C(OMe)_2$/CSA/CH_2Cl_2; NBS/$AgNO_3$/2,6-lutidine/aq MeCN, d) K_2CO_3/MeOH; DIBAH/PhMe; NaH/CS_2/MeI/THF; n-Bu_3SnH/AIBN/PhMe/reflux, e) n-Bu_4NF/THF; $(COCl)_2$/DMSO/CH_2Cl_2; $Ph_3P^+MeBr^-$/n-BuLi/THF/-78~0°C, f) aq AcOH; MeI/KH/THF

(4S,6S,8S,10S,12R,14R,16R,18R,20R)-nonamethoxyl compound **2**, $[\alpha]_D^{24}$ +3.6° (c 0.87, $CHCl_3$), in 88% yield.[17] Since the natural product **2** has been obtained only as a mixture of three homologues,[3] direct comparison of the synthetic compound with the natural one can not be achieved in principle. However, the compound having the stereostructure **2** claimed by Moore was synthesized unequivocally since there is no ambiguity on assigning the stereostructure of chiral centers introduced throughout the present synthesis.

Acknowledgement: We are grateful to Prof. W. Hertz (The Florida State Univ.) for providing 270 MHz ^{1}H-NMR data of natural **1**. We also thank to Prof. M. Nakagawa and Mrs H. Seki (Chiba Univ.) for measuring 270 MHz ^{1}H-NMR spectrum of the synthetic **1**. This work was supported in part by a Grant-in-Aid for Special Research from the Ministry of Education, Science, and Culture "Chemical Syntheses for Elucidation of Biological Functions".

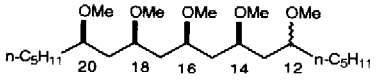
References and Notes

1) T. Nakata, T. Suenaga, and T. Oishi, Tetrahedron Lett., preceding paper.
2) W. Herz and G. Ramakrishnan, Phytochemistry, **17**, 1327 (1978).
3) J. S. Mynderse and R. E. Moore, Phytochemistry, **18**, 1181 (1979).
4) T. Nakata, N. Hata, K. Iida, and T. Oishi, Tetrahedron Lett., **28**, 5661 (1987).
5) Aldehyde **3** was prepared from (2S)-4-t-butyldiphenylsilyloxy-1-butene oxide[1] in 4 steps; 1) n-$C_{14}H_{29}$MgBr/CuI/THF (95%), 2) DHP/CSA/CH_2Cl_2, 3) n-Bu_4NF/THF, 4) PCC/CH_2Cl_2 (77%, 3 steps).
6) The numberings are based on those of natural products **1** and **2**.
7) W. C. Still and C. Gennari, Tetrahedron Lett., **24**, 4405 (1983). (E)-isomer (9%).
8) CD curve: $[\theta]_{300}$ 0, $[\theta]_{255.5}$ -5807, $[\theta]_{235.5}$ -3075, $[\theta]_{229.5}$ -4441, $[\theta]_{226}$ -6521.
9) In this reaction, formation of bicyclic lactone **25** is observed in some cases together with **1** via intramolecular Michael addition. Transformation of **1** to **25** took place easily even on standing of crystalline **1** at rt.



25

10) H. C. Brown and P. K. Jadhav, J. Am. Chem. Soc., **105**, 2092 (1983).
11) The ratio of **14** and the epimer was 0.88 : 1 in ether. It is reported to give high syn-selectivity when ether was used as a solvent.[10]
12) The products were converted to pentamethoxyl compounds **26a,b**. The NMR spectrum of **26a** from the major isomer **14** exhibits signals due to the highly symmetrical compound, confirming that **14** has 12,14-syn configuration:



26a,b

12,14-syn-**26a** (major): ^{1}H-NMR δ 3.31 (s, 3xMe), 3.32 (2xMe), ^{13}C-NMR δ 38.00, 38.29 (C-7,9,11,13). 12,14-anti-**26b** (minor): ^{1}H-NMR δ 3.30 (s; Me), 3.31 (s, 2xMe), 3.35, 3.34 (each s; Me), ^{13}C-NMR δ 38.00, 38.40, 38.73, 40.07 (C-7,9,11,13).

13) T. Oishi and T. Nakata, Acc. Chem. Res., **17**, 338 (1984).
14) Ketone **15** was prepared from (3S)-3,4-O-isopropylidene-3,4-dihydroxybutanal in 4 steps; 1) LDA/MeCOO-t-Bu/THF/-78°C (78%), 2) $LiAlH_4$/THF/0°C, 3) t-$BuPh_2SiCl$/imidazole/DMF/rt (78%; 2 steps), 4) $(COCl)_2$/DMSO/CH_2Cl_2/-78°C (98%).
15) The selectivity of this reduction depends on the solvent used; 6.2 : 1 (ether, 0°C), 8.9 : 1 (CH_2Cl_2, 0°C), 9.6 : 1 (hexane, 0°C), 1.8 : 1 (THF, 25°C).
16) Cf., Y. Mori, M. Kuhara, A. Takeuchi, and M. Suzuki, Tetrahedron Lett., **29**, 5419 (1988).
17) 500 MHz ^{1}H-NMR ($CDCl_3$) δ 3.306, 3.309, 3.313, 3.315, 3.341 (9xMeO); 25 MHz ^{13}C-NMR ($CDCl_3$) δ 14.08, 22.69, 24.64, 32.09, 33.49, 37.66, 37.74, 37.98, 38.25, 56.22, 56.42, 75.37, 75.52, 77.40, 77.98, 117.28, 134.48.

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