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SYNTHESIS OF OPTICALLY ACTIVE MEVINIC ACID SUBUNITS VIA ACETAL INITIATED/VINYLSILANE TERMINATED POLYENE CYCLIZATIONS.

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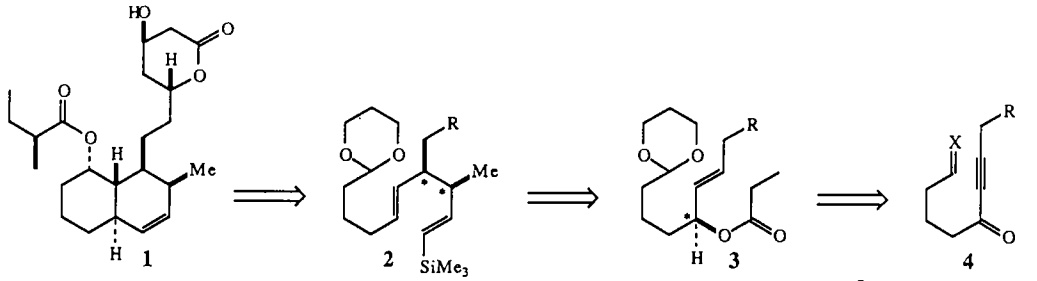
Abstract: Efficient routes to optically active octahydronaphthalenol mevinic acid subunits via vinylsilane-mediated polyene cyclizations initiated by trimethylenedioxy acetals are detailed. Enantioselective alkynone reductions and Ireland-Claisen rearrangements serve to establish and transfer absolute stereochemistry.

We previously reported[2] a synthetic route to the octahydronaphthalenol subunit of dihydrocompactin (1) featuring an acylium ion initiated/vinylsilane terminated polyene cyclization.[3] For this strategy to be generally applicable to the synthesis of the biologically important mevinic acids,[4] several limitations of the prototype sequence required modification. Specifically, we sought (1) a more efficient construction of the polyene cyclization precursor in (2) optically active form with (3) a more effective initiating group. The two sequences described herein, accommodating primitive and more elaborate hydroxy lactone side chain precursors, successfully demonstrate these modifications.

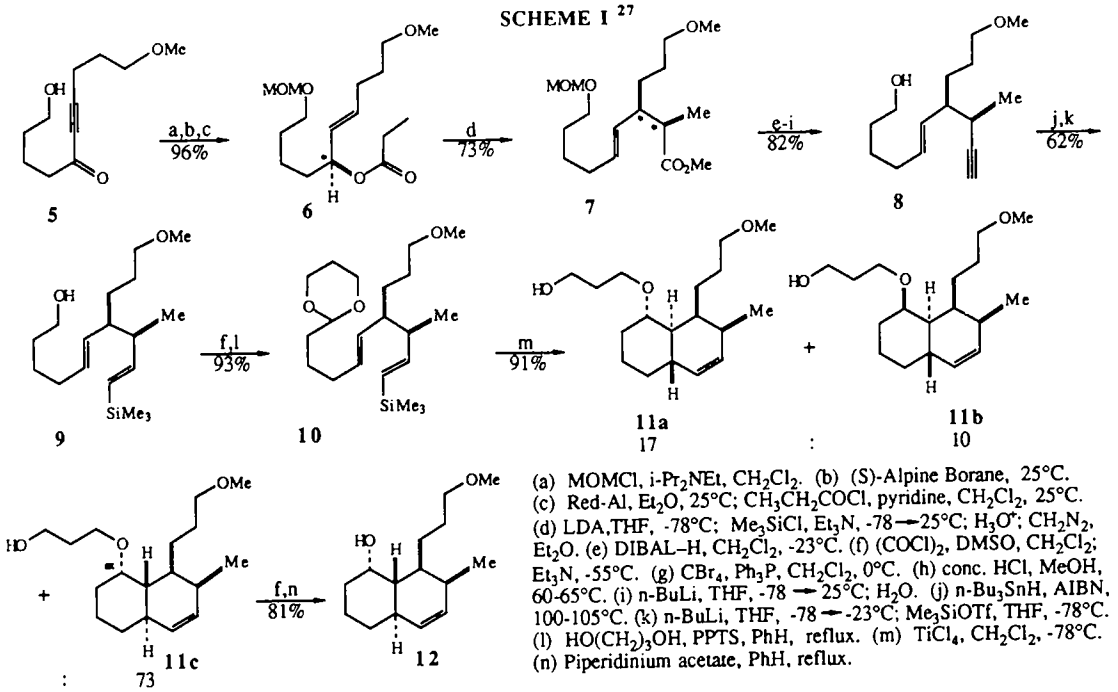


(1)

As summarized antithetically in eq 1, a 1,3-dioxolane acetal initiator[5] replaced the previously utilized[2] acid chloride functionality. The polyene cyclization substrate 2 was thus improved to a stable, isolable substance at the correct oxidation level relative to the hydronaphthalenol portion of 1. Furthermore, we expected 2 to cyclize upon treatment with milder Lewis acids than those required ($SbCl_5$, SbF_5) for the acid chloride initiated cyclization.[6] Control over the relative stereochemistries at the indicated (*) centers in 2 was to be accomplished via Ireland-Claisen rearrangement[7] of ester 3, transferring absolute stereogenicity from the allylic carbinol derived from a Midland[8] or Noyori[9] reduction of the alkynone 4.

The synthesis of the optically active octahydronaphthalenol subunit 12 with a simple methoxypropyl side chain is detailed in Scheme I. Treatment of 1-methoxy-4-pentyne[10] with n-BuLi in tetrahydrofuran (THF) at 0°C followed by addition at -78°C of δ-valerolactone gave in 93% yield the achiral acetylenic ketone 5. Protection of the hydroxyl group as the methoxymethyl ether and asymmetric reduction of the ketone using Midland's method as modified by Brown[8] (2 equiv S-Alpine Borane,[11], neat, 25°C, 18 h) gave the (S)-propargylic alcohol in enantiomeric

SCHEME I [27]

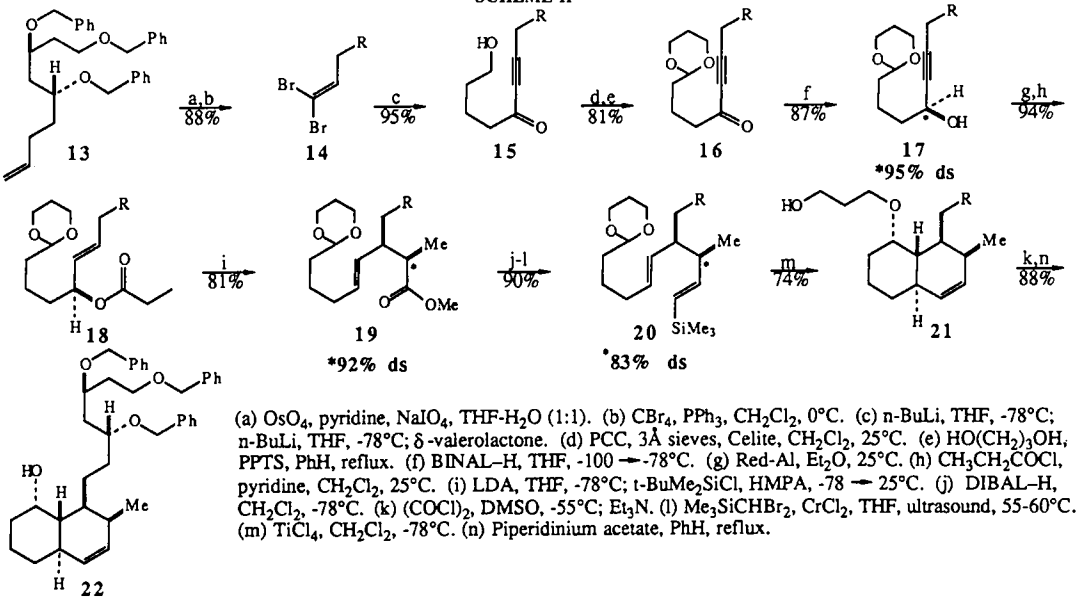


(a) MOMCl, i-Pr_2NEt, CH_2Cl_2. (b) (S)-Alpine Borane, 25°C. (c) Red-Al, Et_2O, 25°C; CH_3CH_2COCl, pyridine, CH_2Cl_2, 25°C. (d) LDA,THF, -78°C; Me_3SiCl, Et_3N, -78→25°C; H_3O^+; CH_2N_2, Et_2O. (e) DIBAL-H, CH_2Cl_2, -23°C. (f) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N, -55°C. (g) CBr_4, Ph_3P, CH_2Cl_2, 0°C. (h) conc. HCl, MeOH, 60-65°C. (i) n-BuLi, THF, -78→25°C; H_2O. (j) n-Bu_3SnH, AIBN, 100-105°C. (k) n-BuLi, THF, -78→-23°C; Me_3SiOTf, THF, -78°C. (l) $HO(CH_2)_3OH$, PPTS, PhH, reflux. (m) $TiCl_4$, CH_2Cl_2, -78°C. (n) Piperidinium acetate, PhH, reflux.

excesses ranging from 77-82%.[12] Reduction with Red-Al[13] to the E-allylic alcohol and esterification with propionyl chloride gave the Claisen rearrangement substrate **6** in 96% overall yield from **5**. Rearrangement[7] of the intermediate E-trimethylsilylketene acetal obtained by kinetic enolate generation and in situ trapping with chlorotrimethylsilane[14] gave the ester **7** as a 13:1 diastereomeric mixture.[15] Conversion of the ester to the aldehyde, Corey-Fuchs[16] homologation, and cleavage of the MOM-ether gave the acetylenic alcohol **8**, in 82% overall yield. The E-vinylsilane **9** was obtained by the cis-addition of tributyltin hydride to the alkyne, transmetallation (4 equiv n-BuLi, -78° → -23° → -78°C, 1.5 h),and trapping with trimethylsilyl triflate.[17] The cyclization substrate, acetal **10**, was produced in a straightforward manner by Swern oxidation[18] followed by treatment with 1,3-propanediol/cat. pyridinium p-toluenesulfonate[19] in refluxing benzene. Attempted cyclizations under conditions commonly used by Johnson[20] in acetal-initiated polyene cyclizations ($SnCl_4$ in benzene, nitromethane, or dichloromethane) all failed for substrate **10**. However, cyclization occurred rapidly and cleanly when a 0.02 M solution of **10** was treated with 1.5 equiv of $TiCl_4$ in CH_2Cl_2 at -78°C for 5 minutes, producing three products (**11a**, **11b** and **11c**) in a ratio of 17:10:73 in 91% yield. The latter two products were not separable until after cleaving the remnants of the acetal initiator by Swern oxidation[18] and β-elimination.[21] The octahydronaphthalenol **12** thus produced [81%, mp 59-63°C, $[\alpha]_D^{23}$ + 104.3° (c 1.75, $CHCl_3$)] was structurally identical (by ^1H NMR, ^{13}C NMR, IR, MS) to the racemic material previously synthesized in our labs.[2] Analysis of the (R)-(+)-MTPA ester derivative[22] of **12** showed it to have an enantiomeric excess of 78%. An overall yield of 19% from 1-methoxy-4-pentyne underscores the efficiency of this route.

A related sequence (Scheme II) afforded a more elaborate dihydrocompactin precursor **22**, wherein the entire carbon skeleton is assembled with all stereochemical details. The enan-

SCHEME II [27]



(a) OsO_4, pyridine, $NaIO_4$, THF-H_2O (1:1). (b) CBr_4, PPh_3, CH_2Cl_2, 0°C. (c) n-BuLi, THF, -78°C; n-BuLi, THF, -78°C; δ-valerolactone. (d) PCC, 3Å sieves, Celite, CH_2Cl_2, 25°C. (e) $HO(CH_2)_3OH$, PPTS, PhH, reflux. (f) BINAL-H, THF, -100 → -78°C. (g) Red-Al, Et_2O, 25°C. (h) CH_3CH_2COCl, pyridine, CH_2Cl_2, 25°C. (i) LDA, THF, -78°C; t-$BuMe_2SiCl$, HMPA, -78 → 25°C. (j) DIBAL-H, CH_2Cl_2, -78°C. (k) $(COCl)_2$, DMSO, -55°C; Et_3N. (l) $Me_3SiCHBr_2$, $CrCl_2$, THF, ultrasound, 55-60°C. (m) $TiCl_4$, CH_2Cl_2, -78°C. (n) Piperidinium acetate, PhH, reflux.

tiomerically pure hydroxy lactone synthon **13**[23] was subjected to Lemieux-Johnson oxidation[24] followed by homologation to the dibromo olefin **14** via the Corey-Fuchs procedure[16] in 88% overall yield. Treatment of **14** with 2.1 equiv of n-BuLi at -78°C gave after aqueous work-up a quantitative yield of the terminal alkyne. Regeneration of the acetylide (1.1 equiv n-BuLi, THF, -78°C, 1 h) and trapping with δ-valerolactone gave in 95% yield the alkynone **15**. The trimethylenedioxy acetal cyclization initiator was introduced in a direct manner to give **16**, which proved to be a poor substrate for the Alpine Borane reduction,[8] in contrast to the substrate in Scheme I. Fortunately, the use of Noyori's (S)-BINAL-H reagent[9] gave the desired product **16** in high yield (87%) and diastereoselectivity (95%). Conversion to the trans allylic alcohol with Red-Al[13] and acylation with propionyl chloride gave the Ireland-Claisen rearrangement[7] substrate **18** in 94% overall yield. Considerable problems with C-silylation of the ester enolate in the rearrangement to **19** were overcome by adding HMPA to the enolate (1.2 mL/mmol), followed by 4 equiv of t-butyldimethylsilyl chloride in THF. The product ester **19** was formed as a 12:1 mixture of diastereomers in 81% yield.

While this work was in progress, Takai reported[25] a one step homologation of aldehydes to E-alkenylsilanes utilizing a gem-dichromium reagent derived from dibromo(trimethylsilyl)methane. If applicable to the α-chiral aldehyde derived from **19**, this method would save three steps over that used to establish the vinylsilane moiety in **9** (Scheme I). Unfortunately, treatment of the derived aldehyde with 2 equiv of dibromo(trimethylsilyl)methane and 8 equiv of chromium(II) chloride in THF at 25°C for 24 h as described by Takai[25] caused substantial epimerization at the indicated stereocenter. However, the reaction proceeded cleanly and gave exclusively the E-vinylsilane terminus. Seeking to minimize the epimerization problem by speeding up this heterogeneous reaction, we found that the reaction time could be reduced to 50 minutes by immersing the reaction flask in an ultrasonic cleaning bath at 55-60°C.[26] Cyclization substrate **20** was thus produced in 90% overall yield with a lessened extent of epimerization.

The vinylsilane-mediated bicyclization was effected by adding a 0.01 M solution of acetal **20** in CH_2Cl_2 to a 0.04 M solution of $TiCl_4$ (4 equiv) in CH_2Cl_2 at -78°C. After 5 minutes the reaction was quenched with MeOH; standard work-up and chromatography gave in 74% yield the trans-fused bicyclic **21**, contaminated with a small amount of inseparable minor isomer(s). Cleavage of the hydroxypropyl group as previously described[21] gave in 88% overall yield the dihydrocompactin precursor **22**. The conversion of **13** to **22** required fifteen synthetic steps and proceeded in 26% overall yield.[27]

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REFERENCES AND NOTES

1. Recipient of a National Science Foundation Presidential Young Investigator Award (1984-89); Research Fellow of the Alfred P. Sloan Foundation (1984-88). Address correspondence to this author at the Department of Chemistry, University of Wisconsin-Madison, Madison, WI 53706.
2. Burke, S. D.; Saunders, J. O.; Oplinger, J. A.; Murtiashaw, C. W. Tetrahedron Lett. **1985**, 26, 1131.
3. For an excellent review of vinylsilane-terminated cyclizations, see: Blumenkopf, T. A.; Overman, L. E. Chem. Rev. **1986**, 857.
4. For a review of synthetic efforts in this area, see: Rosen, T.; Heathcock, C. H. Tetrahedron **1986**, 42, 4909.
5. For a detailed discussion of olefin cyclizations with acetal and non-acetal initiators, see: Bartlett, P.A. In "Asymmetric Synthesis", Morrison, J. D., Ed.; Academic Press: New York 1984; Vol. 3, p. 341.
6. Control experiments indicated that several candidate hydroxy lactone synthons could not survive exposure to such harsh Lewis acids.
7. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. **1976**, 98, 2868. (b) Ireland, R. E.; Mueller, R. H. Ibid. **1972**, 94, 5897.
8. (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. J. Am. Chem. Soc. **1980**, 102, 867. (b) Brown, H. C.; Pai, G. G. J. Org. Chem. **1982**, 47, 1606.
9. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. J. Am. Chem. Soc. **1984**, 106, 6717.
10. From 4-pentyne-1-ol: Ciucanu, I.; Kerek, F. Carb. Res. **1984**, 131, 209.
11. Trade name of the Aldrich Chemical Company. β-Isopinocampheyl-9-borabicyclo[3.3.1]nonane from (-)-α-pinene.
12. Determined by glass capillary GC analysis (Superox-4, 225°C) of the (R)-(+)-MTPA ester.[22]
13. The chemical name for Red-Al (Aldrich Chemical Co.) is sodium bis(2-methoxyethoxy)aluminum hydride. See: Denmark, S. E.; Jones, T. K. J. Org. Chem. **1982**, 47, 4595.
14. Corey, E. J.; Gross, A. W. Tetrahedron Lett. **1984**, 25, 495.
15. Ratio determined by capillary GC analysis.
16. Corey, E. J.; Fuchs, P. L. Tetrahedron Lett. **1972**, 3769.
17. Attempted formation of the trans-vinylsilane by hydroalumination/protonolysis of the trimethylsilyl acetylene as reported by Eisch (Eisch, J. J.; Damasevitz, G. A. J. Org. Chem. **1976**, 41 2214) gave instead the cis-vinylsilane. Diagnostic ^{1}H NMR couplings of $^3J_{cis}$ = 14 Hz and $^3J_{trans}$ = 18.6 Hz were observed for the geometric isomers.
18. Mancuso, A.; Huang, S.-L.; Swern, D. J. Org. Chem. **1978**, 43, 2480.
19. Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. J. Org. Chem. **1977**, 42, 3772.
20. Johnson, W. S. Bioorg. Chem. **1976**, 5, 51.
21. Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. J. Am. Chem. Soc. **1984**, 106, 7588.
22. Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. **1969**, 34, 2543.
23. Prepared in two steps (91%) from the known compound [4(R)-cis]-6-(2-benzyloxy)ethyl-4-(3-butenyl)-2,2-dimethyl-1,3-dioxane (Hirama, M.; Uei, M. J. Am. Chem. Soc. **1982**, 104, 4251): (i) 1 N HCl, THF, 25°C, 3 h. (ii) NaH, n-Bu_4NI, $PhCH_2Br$, THF, reflux.
24. Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. J. Org. Chem. **1956**, 21, 478.
25. Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. Tetrahedron Lett. **1987**, 28, 1443.
26. For an excellent review of the use of ultrasound in chemistry, see: Suslick, K. S. In "Modern Synthetic Methods 1986", Scheffold, R., Ed.; Springer-Verlag: Berlin 1986, p. 1.
27. Yields cited in the Schemes are for chromatographically pure substances. All structural assignments are supported by high-field ^{1}H NMR, ^{13}C NMR, IR, MS and combustion analyses.

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