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BIFUNCTIONAL CYCLOPROPYL REAGENTS: A TOTAL SYNTHESIS OF 7-E,9-Z METHYL TRISPORATE B[1]

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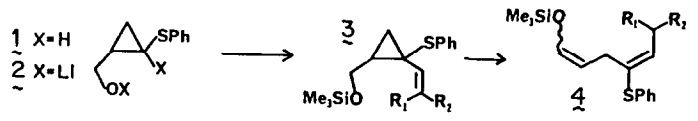
SUMMARY: 2-Hydroxymethylcyclopropyl phenyl sulfide combined with sulfenylation-dehydrosulfenylation permits a stereo- and chemoselective approach to trisporic acids.

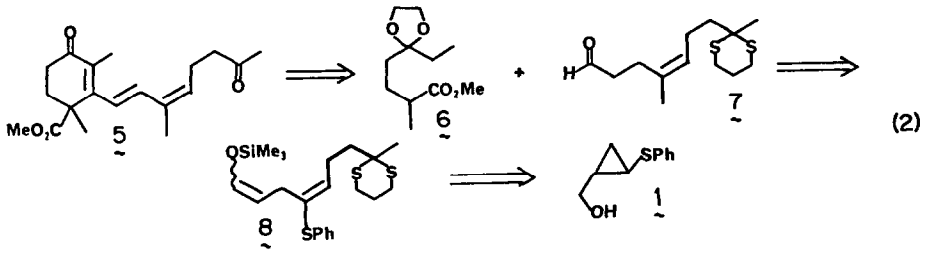
We have shown that the bifunctional cyclopropane 1[2] as its lithium dianion 2 is a useful synthon for the preparation of a variety of chemodifferentiated dienes 4 of defined stereochemistry with respect to the vinyl sulfide via the intermediacy of vinyl cyclopropyl siloxanes 3 (eq 1). Herein we wish to report



(1)

the use of the bifunctional reagent 2 in a total synthesis of the fungal prohormone 9Z (and 9E) methyl trisporate B[3] (5, R=CH_3).

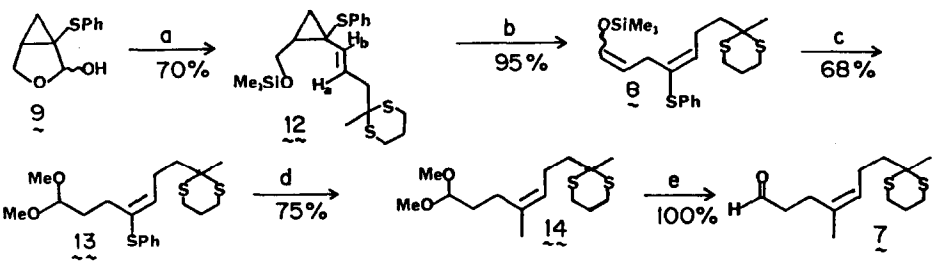
Equation 2 represents a retrosynthetic analysis in which the key aspect envisions that a suitably functionalized diene 8 could serve as the source of the 9-Z side chain 7 of methyl trisporate B and that sulfenylation-dehydrosulfenylation could introduce the 7E olefin.[4]



(2)

The protected β-ketoester portion 6 was prepared simply in 3 steps and 67% overall yield by 1) Michael addition of dimethyl methylmalonate to ethyl vinyl

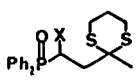
SCHEME I



(a) i: 11, THF, -78° to rt; ii: H_3O^+; iii: KH, THF, reflux; iv: $(CH_3)_3SiCl$, C_5H_5N, ether, rt. (b) FVP, 60°C, 0.005 torr. (c) CH_3OH, $(CH_3O)_3CH$, HCl (from $POCl_3$), -10°C to 0°C. (d) CH_3MgBr, $(dppp)NiCl_2$, THF, ether, reflux. (e) CH_3CN, HCl, H_2O, rt.

ketone (5% KOtBu, THF, 0°C to rt), 2) formation of the ethylene ketal ($HOCH_2CH_2OH$, C_6H_6, p-TSA, $-H_2O$) and 3) decarbomethoxylation (KOAc, DMSO, 160°C). The only purification that was required was a simple distillation of the ester 6 (b.p. 87-93°C, 0.03 torr)[6,7].

Preparation of the requisite Z-olefinic side chain aldehyde 7 was accomplished in 5 steps from the previously reported lactol 9[3] (Scheme I). Condensation of 9 with the lithio derivative 11 (n-BuLi, THF, -78°C) of the phosphine oxide 10[8,9] afforded an intermediate hydroxy phosphinate, which was

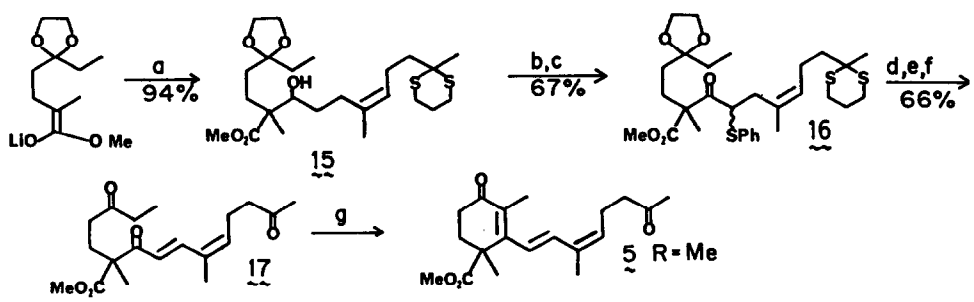


10 X=H
11 X=Li

heated with excess potassium hydride in THF (to effect elimination of diphenyl phosphinic acid) and then silylated to give the desired vinyl cyclopropane 12[5,6] in 70% yield from 9. The all-E nature of the olefin in 12 was verified by observation of a 15.5 Hz coupling constant between protons H_a and H_b[6,8]. Flash vacuum pyrolysis[9] of 12 afforded in 95% yield a 7:3 mixture (by 270 MHz NMR) of the E,E and Z,E dienes 8[6] which were directly transformed into the vinyl sulfide acetal 13[5] in 68% yield. Coupling with methylmagnesium bromide[16] in the presence of 5 mol% $(dppp)NiCl_2$[10c] (THF, ether, reflux) gave cleanly a 75% yield of the olefin 14[5,6], whose stereohomogeneity was verified by 15.04 MHz ^{13}C and 270 MHz ^1H NMR. Hydrolysis yielded quantitatively the desired aldehyde 7[5,6].

The coupling of these two fragments and final elaboration to 5 (R=Me) proceeded as outlined in Scheme II. Generation of the lithium enolate of

SCHEME II



(a) 7, THF, -78°C. (b) DMSO, Ac_2O, rt. (c) i: $KN[Si(CH_3)_3]_2$, DME, 0°C to rt; ii: PhSSPh, 0°C. (d) i: $HgCl_2$, CH_3CN, H_2O, THF, rt; ii: 10% HCl, CH_3CN. (e) MCPBA, CH_2Cl_2, -78°C. (f) CCl_4, ethylvinyl ether, (2:1), 60°C. (g) $PhCH_2N(CH_3)_3^+ \ ^-OCH_3$, CH_3OH, -10°C to 0°C.

6 (LDA, THF, -78°C) and subsequent addition of 7 gave a 94% yield of the desired aldol 15[5,6] as a 1:1 mixture of diastereomers (by NMR). Oxidation of 15 yielded a selectively protected triketoester which was cleanly sulfenylated[4] with potassium hexamethyldisilazide and diphenyldisulfide in DME to give the desired β-ketosulfide 16[5,6] (again a 1:1 mixture of diastereomers) in 67% yield from 15. Deprotection of the dithiane and ketal moieties, followed by oxidation to the sulfoxide[4] and pyrolysis[4], yields only the 7-E,9-Z (trisporate numbering) triketodienone 17[5,6], in 66% yield for the three steps. Finally, treatment of 17 with excess benzyl trimethylammonium methoxide in methanol (-10°C, 1.5 hr; 0°C, 5.5 hr) gave a 22% yield of 5 as a 3:1 mixture of 9-Z and 9-E isomers, respectively. The mixture was separated by HPLC[11] and each isomer showed NMR and IR data that was identical to data previously reported for methyl trisporate B.

The bifunctional cyclopropyl reagent provided an efficient stereocontrolled five step synthesis of the side chain of methyl trisporate in 34% overall yield. In addition, the sulfenylation-dehydrosulfenylation served as a stereo- and chemoselective sequence for introduction of the 7E double bond in excellent yield. The flexibility offered by these methods under development in our laboratories combines with a convergent strategy to the fungal prohormones which permits access to analogs for biological evaluation.

Acknowledgment. We wish to thank the National Science Foundation for their generous support of our programs.

References & Notes

1. Taken in part from the Ph.D. thesis of Ornstein, P.L., University of Wisconsin, Madison, 1982

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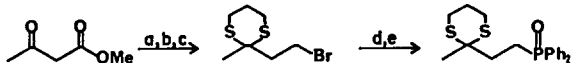
5. All new compounds were characterized by IR, NMR and mass spectroscopy, and elemental composition established by combustion analysis and/or high-resolution mass spectroscopy.

6. Selected IR and NMR data: 7: IR ($CDCl_3$) 2960, 2820, 2720, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.79 (s, 1H), 5.91 (t, J=7.0 Hz, 1H), 2.85 (m, 4H). 2.52 (m, 2H), 2.38 (m, 2H), 2.18 (m, 2H), 1.96 (m, 4H), 1.69, (s, 3H), 1.62 (s, 3H). 6: IR ($CDCl_3$) 2960, 2850, 1225, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 3.93 (s, 4H) 3.67 (s, 3H), 2.44

(sextet, J=7.0 Hz, 1H), 1.43-1.80 (m, 8H), 1.16 (d, J=7.0 Hz, 1H), 0.89 (t, J=7.5 Hz, 3H). 10: IR ($CDCl_3$) 3050, 2900, 1590, 1480, 1430 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-7.8 (m, 10H), 2.25-2.90 (m, 8H), 1.96 (m, 2H), 1.65 (s, 3H). 12: IR ($CDCl_3$) 3060, 2950, 1585, 1475, 1435 cm^{-1}. ^1H NMR ($CDCl_3$)δ: 7.05-7.51 (m, 5H), 5.77 (m, 1H), 5.67 (d, J=15.4 Hz, 1H), 3.76 (dd, J=15.4 Hz, 1H), 3.51 (dd, J=11.2, 8.3 Hz, 1H), 2.78 (m, 4H), 2.63 (m, 2H), 1.92 (m, 2H), 1.73 (m, 1H), 1.41 (s, 3H), 1.30 (dd, J=8.8, 5.2 Hz, 1H), 1.10 (t, J=5.9 Hz, 1H), 0.13 (s, 9H). 14: IR ($CDCl_3$) 2920, 2820, 1440 cm-1. ^1H NMR ($CDCl_3$)δ: 5.16 (t, J=7.0 Hz, 1H), 4.34 (t, J=5.7 Hz, 1H), 3.32 (s, 6H), 2.84 (m, 4H), 2.23 (m, 4H), 1.85 (m, 4H), 1.69 (s, 3H), 1.66 (m, 2H), 1.61 (s, 3H). ^{13}C NMR ($CDCl_3$) 134.9 124.5, 103.9, 52.4, 48.9, 41.5, 30.6, 27.6, 26.6, 26.3, 25.2, 23.1. 15: IR ($CDCl_3$) 3520, 2940, 1720, 1600, 1450, cm^{-1}. ^1H NMR ($CDCl_3$)δ: 5.18 (t, J=6.8 Hz, 1H), 3.93 and 3.92 (s, 4H), 3.70 and 3.68 (s, 3H), 3.65 (m, 1H), 2.85 (m, 4H), 1.15-2.50 (m, 17H), 1.69 (s, 3H), 1.62 (s, 3H), 1.12 (s, 3H), 0.88 (m, 3H). 16: IR ($CDCl_3$) 2970, 1735, 1710, 1590, 1465 cm^{-1}. ^1H NMR ($CDCl_3$)δ: 7.26-7.48 (m, 5H), 5.19 (m, 1H), 4.18 (m, 1H), 3.91 (s, 4H), 3.67 (s, 3H), 1.31-2.98 (m, 18H), 1.66 and 1.61 (s, 3H), 1.53 (s, 3H), 1.36 and 1.39 (s, 3H), 0.88 (m, 3H). 17: IR ($CDCl_3$) 2970, 1715, 1690, 1625. 1590. 1450 c,$^{-1}$. ^1H NMR ($CDCl_3$)δ: 7.78 (d, J=15.1 Hz, 1H), 6.25 (d, J=15.1 Hz, 1H), 5.80 (m, 1H), 3.72 (s, 3H), 2.56 (m, 4H), 2.43 (q, J=7.4 Hz, 2H), 2.40 (m, 2H), 2.16 (m, 2H), 2.16 (s, 3H), 1.83 (s, 3H), 1.38 (s, 3H), 1.04 (t, J=7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) : 210.0, 207.1, 196.2, 173.5, 139.9, 139.4, 131.8, 121.3, 57.7, 52.4, 43.2, 37.3, 35.9, 29.8, 28.8, 22.2, 20.0, 19.4, 7.8.

7. The phosphine oxide 11 was prepared as shown in 53% overall yield (mp. 117-118.5°C):



11

a: $HS(CH_2)_3SH$, $BF_3{\cdot}O(C_2H_5)_2$, $CHCl_3$, 0°C to rt; b: $LiAlH_4$, ether, 0°C. c: $Ph_3P{\cdot}Br_2$, CH_2Cl_2, C_5H_5N, 0°C; d: Ph_3P, C_7H_8, reflux; e: 15% aq NaOH, reflux.

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11. Waters M. 6000 A analytical HPLC, 5 radially compressed column, 14% ethyl acetate/hexane, 2.0 mL/min, t_r=33.3 min for the 9-E isomer, 35.5 min for the 9-Z isomer.

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