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CONVENIENT ACCESS TO TWO ENANTIOMERIC OXIRANE SYNTHONS BEARING A QUATERNARY GEM-DIMETHYL CARBON CENTER: SYNTHESIS OF 3S-(+) and 3R-(-)-2,2-DIMETHYL-3,4-OXO-1-BUTANOL FROM R-(-)-PANTOLACTONE.

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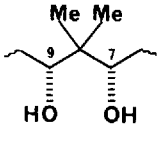
ABSTRACT: Starting with the commercially available R(-)-Pantolactone and using three different pathways, the synthesis of two new and potentially useful enantiomeric hydroxy epoxide synthons possessing a quaternary gem-dimethyl carbon center is reported.

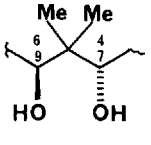
Over the years, an increasing number of structurally and biologically interesting natural products possessing a quaternary gem-dimethyl carbon center has been reported. Among these compounds, one would notice that Aplasmomycin[2a], Boromycin[2b], Goldinonic Acid[2c], the Bryostatins[2d], Acutiphycin[2e] and Pederol[2f] are all bearing at least one quaternary center which is flanked on both sides (α and α') by either one carbonyl group (α) and one chiral carbinolic center (α') or two chiral carbinolic centers (α and α') (Scheme 1).

Enantiomeric approaches to these challenging natural products, or fragments thereof, could represent a certain degree of difficulty considering: a) the limited availability of readily accessible chiral starting materials possessing a quaternary gem-dimethyl center, and b) the existing methodology for the construction of such a center[3] adjacent to chiral carbinolic appendages.

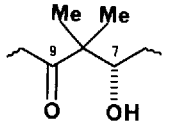
Scheme 1



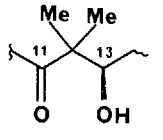
Aplasmomycin
Boromycin
(North)



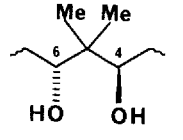
Goldinonic Acid
Boromycin
(South)



Bryostatins



Acutiphycin



Pederol

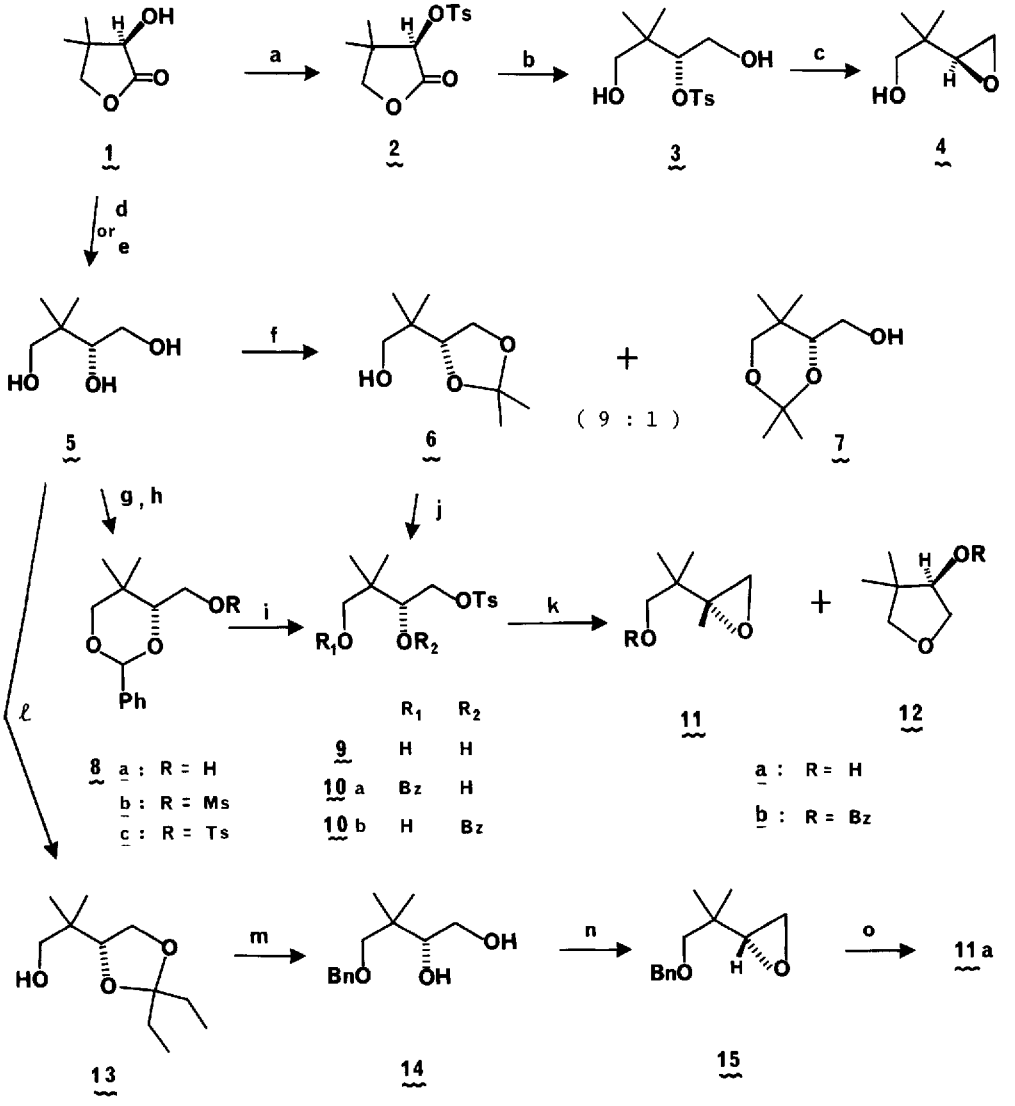
It then came to our attention that the commercially available R(-)-Pantolactone 1, a degradation product of pantothenic acid, was indeed an ideal precursor that would allow us to develop a general and versatile enantio-divergent synthetic strategy. Supplementing to the already flourishing chiron pool[4], we describe here two short and efficient routes to the enantiomeric 4-hydroxy oxiranes 4 and 11a from (-)-1.

In the first and quite expeditious sequence (see Scheme 2 for experimental details), tosylation of 1 followed by reduction of 2 [mp 98-99°C, $[\alpha]_D^{25}$ - 22.1° (c 2, $CHCl_3$)] with excess DIBAH at 0°C and quenching with $Na_2SO_4 \bullet 10H_2O$ [5] gave the nicely crystalline diol 3 [mp 79-80°C, $[\alpha]_D^{25}$ + 4.9° (c 2, $CHCl_3$)]. Treatment of 3 with a premixture (4h, 25°C) of K_2CO_3 in MeOH provided, with inversion of configuration at C-3, the (+)-hydroxy oxirane 4 ($[\alpha]_D^{25}$ + 16.0° (c 2, EtOAc)) in over 90% yield after distillation (bp 70°C/1.3 mm) [Phenylurethane derivative, mp 48°C, $[\alpha]_D^{25}$ + 10.3° (c 2, EtOAc)].

In the second sequence (Scheme 2), 1 was reduced with either excess $LiAlH_4$ or with excess $BH_3 \bullet Me_2S$-cat.$NaBH_4$ [6a] to the corresponding triol 5 [7] [oil, $[\alpha]_D^{25}$ - 15.0° (c 2, EtOH)]. Formation of the acetonide 6 proceeded very rapidly (but only when boron-free 5 was used)[6b] to afford a 9:1 mixture (GLC) of 6 and dioxane ketal 7 as confirmed by various methods.[8] Alternatively, 5 was converted [9] nearly exclusively to the 1,3-benzylidene 8a, from which the derivatives 8b (oil) and 8c [mp 81-82°C, $[\alpha]_D^{25}$ - 18.6° (c 2, $CHCl_3$)] were obtained as usual (RSO_2Cl, pyr. 25°C, 80%). Surprisingly, when either 8c (or 8b) was submitted to various acidic or hydrogenolysis conditions required for the cleavage of the benzylidene acetal, none of the expected sulfonate diol 9 could be isolated from the complex reaction mixture. Only ozonolysis[10] gave, as expected, a mixture of 10a and 10b (major), the later being converted (>80%) (via 1,3-acyl migration) to 10a under mild acidic conditions during work-up ($NaHSO_3$). Alternatively, 10a was also obtained in 3 steps (60%) from purified 6 (j. Scheme 2). Unfortunately, basic treatment of pure 10a (MeONa or K_2CO_3/MeOH, 0° to 25°C) gave an inseparable (flash, distillation) mixture of the desired oxirane 11a (major) and 12a. Even quite delicate conditions (k, 1°, Scheme) invariably would give 11b ($[\alpha]_D^{25}$ - 11.2° (c 3.7, $CHCl_3$) in 80-85% yield (and easily debenzoylated to 11a) in addition to 10-15% of 12b ($[\alpha]_D^{25}$ + 105.4° (c 1.7, $CHCl_3$)) after a careful chromatographic separation, which by no means made this sequence convenient.

Finally, a more practical and efficient sequence was devised. Treatment of 5 with 3-pentanone (l, Scheme) gave exclusively the 1,2-diol 3-pentylidene[11] derivative 13 [>90%, bp 69°C/15 mm, $[\alpha]_D^{25}$ - 4.6° (c 2.1, $CHCl_3$)] which, after benzylation and mild acid hydrolysis of the dioxolane ketal yielded the crystalline benzyl diol 14 [85%, mp 55°C, $[\alpha]_D^{25}$ - 9.4° (c 2, EtOAc)]. Sequential treatment of 14 with NaH and Ts-imidazole[12] led to the formation of the benzyl oxirane 15 [80%, bp 96-97°/0.25 mm, $[\alpha]_D^{25}$ - 9.7° (c 2.7, EtOAc); (+)-15 derived from (+)-4: $[\alpha]_D^{25}$ + 10.2° (c 2, EtOAc)] and subsequent hydrogenolysis of the benzyl group gave the desired (-)-hydroxy oxirane 11a in nearly quantitative yield[13] ($[\alpha]_D^{25}$ -15.2° (c 1.8, EtOAc); phenyluretane derivative: mp 48°C, $[\alpha]_D^{25}$ -10.5° (c 1.1, EtOAc)).

Scheme 2



Reagents[14]: (a) TsCℓ, DMAP cat., pyr., rt (95%). (b) 1° DiBAH, 3 equiv., THF, 0°C; 2° $Na_2SO_4 \bullet 10H_2O$[5] (80%). (c) K_2CO_3, MeOH, rt (90%). (d) 1° $LiAlH_4$, THF, reflux; 2° $Na_2SO_4 \bullet 10H_2O$[5] (95%). (e) $BH_3 \bullet Me_2S$, $NaBH_4$ cat., THF, reflux (80%, boron-free)[6b]. (f) acetone, p-TsOH cat., rt (100%). (g) $PhCH(OMe)_2$, $POCℓ_3$ cat., $CH_2Cℓ_2$, reflux[9]. (h) $RSO_2Cℓ$, pyr. rt (80% from 5). (i) O_3, $CℓCH_2CH_2Cℓ$, AcOH cat., 0°C (95%). (j) 1° BzCℓ, pyr., rt; 2° HCℓ 1M-THF (1:1), rt; 3° TsCℓ, pyr. rt (60%). (k) 1° NaH, DMF-THF (1:1), -20°C; 2° cat. MeONa, MeOH (80%). (ℓ) 3-pentanone, p-TsOH cat., THF, reflux (90%). (m) 1° NaH, $PhCH_2Br$, DMF; 2° 80% aq. AcOH, reflux; 3° cat. MeONa, MeOH (85%). (n) 1° NaH, 2.5 equiv.; 2° Ts-imidazole, THF-DMF (1:1) (80%). (o) H_2, 20% $Pd(OH)_2/C$, 95% EtOH, rt (90%).

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7. (a) T. Matsuo, K. Mori, M. Matsui, Tetrahedron Lett. 1979 (1976). (b) These authors reported for 5 ($LiAlH_4$ reduction of 1, 34%): $[\alpha]_D^{22}$ - 16.0° (c 1, EtOH).

8. (a) After a delicate separation by MPLC (EtOAc-hexane, 1:1), ^{1}H and specially ^{13}C-NMR were quite indicative [8b]: 6, δ 108.9 ppm for the ketal carbon, and 7, δ 98.9 ppm. (b) J.G. Buchanan, A.R. Edgar, D.I. Rawson, P. Shahidi, R.H. Wightman, Carbohydr. Res., 100, 75 (1982). (c) Data for 6: $[\alpha]_D^{25}$ - 1.5° (c 5.6, $CHCl_3$); 3,5-DNBz derivative: mp 50-51°C, $[\alpha]_D^{25}$ + 8.8° (c 3, $CHCl_3$). Lit.[7a] for 6: $[\alpha]_D^{22}$ - 0.7° (neat), and see ref. 2c for other uses of 5 and 6.

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13. Starting with S-(+)-pantolactone derived from S-(-)-dimethyl malate [see: D. Wasmuth, D. Arigoni, D. Seebach, Helv. Chim. Acta. 65, 344 (1982)], the epoxide 11a could also be made available using the sequence 1 to 4 described above.

14. All compounds reported in this paper gave satisfactory spectroscopic (IR, ^{1}H and ^{13}C-NMR) and analytical data (MS and/or microanalysis). The yields reported are for isolated and pure products and were not necessarily optimized.

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