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Bryostatin: a novel asymmetric synthesis of the C_{27}–C_{34} fragment starting from (*R*)-carvone as chiral template

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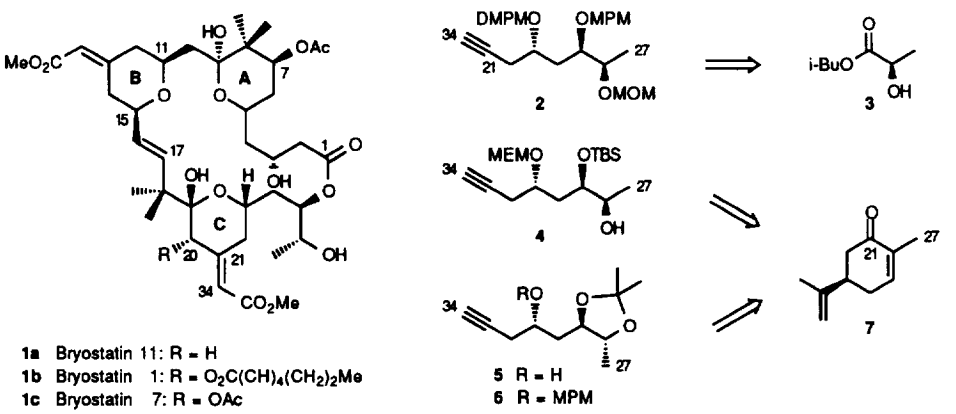
Abstract: (*R*)-Carvone is a suitable chiral template for the synthesis of differently protected (4*S*,6*R*,7*R*)-trihydroxy-1-octyne derivatives, the C_{27}–C_{34} fragment of bryostatins. Also other potentially interesting chiral building blocks are described. © 1997 Elsevier Science Ltd

The bryostatins **1** constitute a family of some 17 highly oxygenated marine macrolides based on a polyacetate-derived backbone (Scheme 1).[1] They exhibit exceptional antineoplastic activity against PS lymphocytic leukemia and ovarian carcinoma.[2] Next to the first completed total synthesis of bryostatin 7(1C) by Masamune *et al.*,[3] other groups have described the synthesis of various fragments of the 20-membered ring lactone.[4–6]



1a Bryostatin 11: R = H
1b Bryostatin 1: R = $O_2C(CH)_4(CH_2)_2Me$
1c Bryostatin 7: R = OAc

Scheme 1.

Previously we have described a synthesis of the C_{17}–C_{27} fragment involving a C_{27}–C_{34} acetylenic intermediate **2** obtained from D-isobutyllactate **3** as the chiral template.[6a,b]

The synthesis of the differently protected eight carbon fragment **6**, starting from L-threonine, has been described by Masamune *et al.*[3b] Intermediate C_{21}–C_{27} fragments has also been obtained by Roy *et al.*[5a] from D-galactonolactone, by Evans *et al.*[5b] *via* Sharpless epoxidation procedure and by Hale *et al.*[5c] *via* a Sharpless asymmetric dihydroxylation–epoxidation sequence.

The present paper describes a new approach for the C_{27}–C_{34} fragment based on (*R*)-carvone **7**[7] as the chiral template, a less obvious starting material for the synthesis of acyclic polyols. The described selective epoxidation of **7** led to **8**.[8] The organoselenium-mediated reductive opening[9] of the epoxide gave the known[10] alcohol **9** next to the 2-epimer in a 4:1 ratio; crystallization from EtOAc–hexane (5:95) led to pure **9**. It has previously been obtained upon lithium liq. ammonia reduction[10] of **8**; the relative C-2, C-3 configuration was fully proven by ^1H NMR and is in accord with literature data.[10]

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Protection of the hydroxy group in **9** was best performed with *tert*-butyldimethylsilyl triflate as the use of TBSCl led to substantial elimination back to **7**.

With **10** in hand we turned our attention to the oxidative removal of the isopropylidene substituent. Originally we had planned to perform a double Baeyer–Villiger oxidation on the corresponding ketone **11** to the desired lactone **14**. However, in the beginning no conditions could be found for cleaving the exocyclic ketone; only oxidation of the cyclic keto function was observed leading to the lactone **13** in 63% yield. A viable route was found *via* ozonolysis of **10** in dry methanol to the methoxy-hydroperoxide which upon treatment with *p*-nitrobenzoyl chloride and *in situ* Criegee rearrangement[12] of the intermediate methoxy-peroxy ester afforded acetate **12**. The reaction conditions are quite critical as traces of water have to be avoided during the whole process.[13b] The mechanism is known[12,13a] to proceed with retention of configuration; the structure of **12** was fully proven by ^{1}H NMR.[11] Baeyer–Villiger oxidation of **12** finally gave our key-intermediate **14**,[11] a C_{21}–C_{27} fragment with the correct stereogenic centers and a carboxyl function as the handle for further chain extention.

In order to avoid the rather critical Criegee rearrangement (**10**→**12**) we decided to reinvestigate the alternative route to **14** based on the double Baeyer–Villiger oxidation of diketone **11**. In the first experiments only oxidation of the cyclic ketone function, leading to **13**, was observed after circa 24 h (*vide supra*). This indicates a much lower reactivity of the exocyclic ketone. Also more powerful reagents[14b] did not lead to expected **14**. Only upon performing the oxidation with 20 eq MCPBA for 6 days the desired product **14** was obtained in 70% yield. This observation deserves some comment. The Baeyer–Villiger oxidation of cyclohexylketones is normally an excellent process[8,14a] and is substantiated with the formation of **24** from **23**. In the transformation of **11** to **14**, the carbonyl function in intermediate **13** is now exocyclic to a 7-membered ring; apparently this ring has a low migratory ability. This bears some parallel with reported problems on the cleavage of straight-chain ketones.[14b] Furthermore to the best of our knowledge only one case of a Baeyer–Villiger oxidation of a cycloheptylketone has been reported.[15]

As can be deduced from Scheme 2 the synthesis of **14** *via* the double Baeyer–Villiger oxidation is the superior one and is furthermore easier to perform.

The most expedient route to an acetylenic C_{27}–C_{34} precursor would involve DIBAH reduction of **14** to the lactol with concomitant deprotection of the 23-hydroxy group followed by *in situ* treatment with diazomethylphosphonate.[16] Unfortunately the reduction step led to substantial decomposition of the β-hydroxy aldehyde.

This forced us to first protect the hydroxy function. Base mediated methanolysis of the acetate in **14** caused decomposition. On the other hand, enzyme catalyzed hydrolysis afforded in high yield alcohol **15**, which was then transformed to **16**. Reduction of **16** to the lactol **17** (in equilibrium with the corresponding aldehyde) followed by treatment of this crude mixture with dimethyl (diazomethyl) phosphonate[15] afforded alkyne **4**.

An alternative route to the differently protected C_{27}–C_{34} fragment **6** involves as intermediate the heptyltetrol **18**, obtained by reduction of **14**. Selective protection of the α-diol unit and of the 3-hydroxy group led to primary alcohol **21**. Oxidation to the aldehyde **22** and formation of the alkyne function, employing the Seyfert reagent,[15] finally afforded the target molecule **6**.

The use of the fragments **2** and **6** (**5**) for bryostatin synthesis has already been documented.[3b,6a,b] These and other described intermediates derived from (*R*)-carvone (or (*S*)-carvone for the enantiomeric series) could be of interest for the synthesis of other natural products possessing a polyol structure.

Acknowledgements

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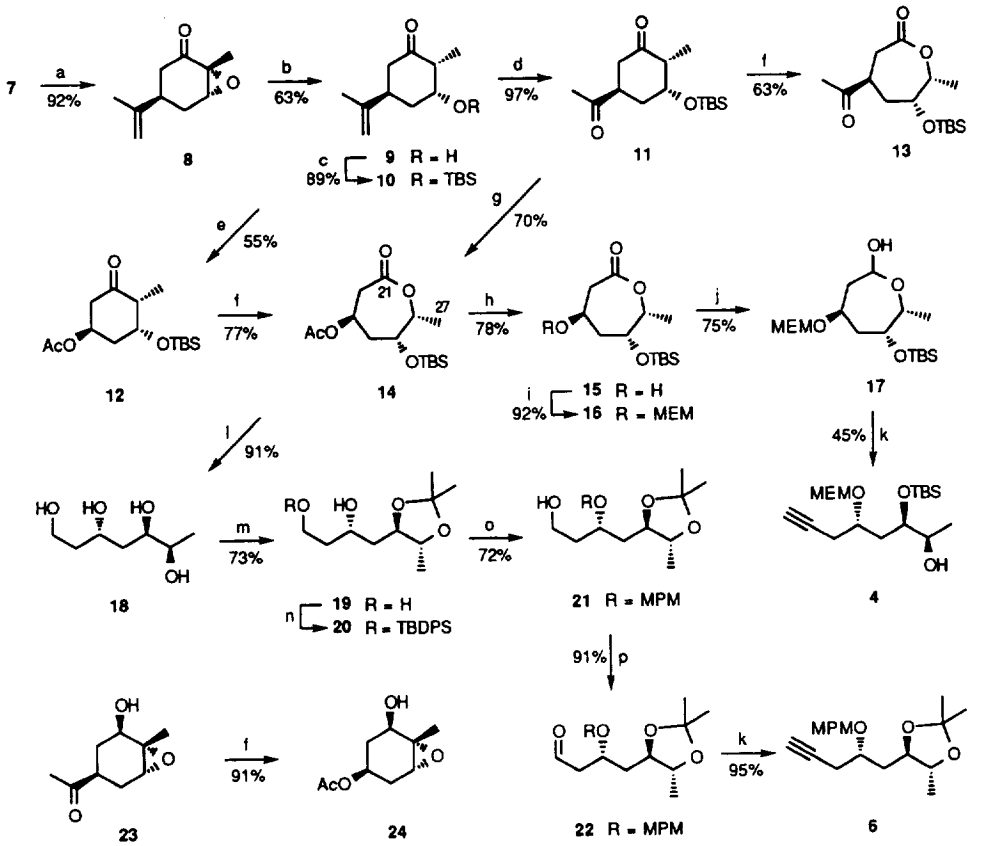

(a) H_2O_2, NaOH, MeOH, -10 °C, 3 h; (b) Ph_2Se_2, $NaBH_4$, EtOH, HOAc, 0 °C, 15 min; (c) TBSOTf, CH_2Cl_2, 2,6-lutidine, 0 °C, 20 min; (d) KIO_4, OsO_4, THF-H_2O (1:1), 12 h; (e) O_3, CH_2Cl_2, MeOH, -78 °C, 40 min; then dry PhH and evaporation; then CH_2Cl_2, py, *p*-$NO_2C_6H_4COCl$, 0 °C, 1 h, Δ 15 h; (f) MCPBA (10 eq), CH_2Cl_2, r.t., 2 d; then Me_2S; (g) MCPBA (20 eq), CH_2Cl_2, r.t., 6 d; then Me_2S; (h) PLE (EC 3.1.1.1), phosphate buffer pH 7, Me_2CO, 35 °C; (i) MEMCl, DIPEA, CH_2Cl_2, r.t., 16 h; (j) DIBAH, CH_2Cl_2, -78 °C, 1 h; (k) $(MeO)_2P(O)CHN_2$, *t*-BuOK, THF, -78 to -30 °C, 12 h; (l) $LiBH_4$, THF, r.t, 6 h; then Amberlyst A-15, MeOH-THF, 1 h; (m) (i) $(MeO)_2CMe_2$, THF, PPTS, r.t., 2 h; (ii) MeOH, PPTS, r.t., 2 h; (n) TBDPSCl, py, DMAP, CH_2Cl_2, 0 °C, 16 h; (o) (i) MPM-trichloroacetimidate, CF_3SO_3H, r.t., 1 h; (ii) TBAF, THF, r.t., 4 h; (p) SO_3.py, Et_3N, DMSO, -10 °C, 4 h.

Scheme 2.

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11. Selected analytical data. **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, d, J=6.7 Hz), 1.84 (1H, ddd, J=12.9, 10.6, 2.1 Hz), 2.04 (3H, s), 2.37 (1H, dddd, J=12.9, 4.5, 4.5, 2.0 Hz), 2.40 (1H, ddd, J=13.8, 10.9, 1.1 Hz), 2.46 (1H, ddq, J=6.7, 2.5, 1.1 Hz), 2.83 (1H, ddd, J=13.8, 5.3, 2.0 Hz), 4.19 (1H, ddd, J=4.5, 2.5, 2.1 Hz), 5.32 (1H, dddd, J=10.9, 10.6, 5.3, 4.5 Hz) ppm. **14**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (3H, d, J=6.7 Hz), 1.8 (1H, ddd, J=2.9, 10, 11.2 Hz), 2.05 (3H, s), 2.28 (1H, dd, J=4.7, 13.5 Hz), 2.91 (2H, d, J=7.7 Hz), 3.92 (1H, dd, J=2.9, 5.4 Hz), 4.48 (1H, q, J=6.7 Hz), 5.35 (1H, dddd, J=5.0, 5.0, 10.3, 15.4 Hz) ppm. $[\alpha]_D^{20}$ values in $CHCl_3$ or otherwise stated for: **4**; +24.8 (c=1.2), **6**; +71.7 (c=1.0), **8**; +1.7 (c=2.0), **9**; −18.6 (c=1.7), **10**; −27.7 (c=2.0), **12**; −14.3 (c=1.7), **14**; +6.0 (c=1.0), **15**; +14.5 (c=1.0), **16**; +29.7 (c=1.0), **18**; +27.6 (c=2.9, MeOH), **19**; +16.9 (c=1.1), **20**; +17.3 (c=1.1), **21**; +25.5 (c=0.8), **22**; +27.6 (c=1.4), **23**; −25.7 (c=1.6), **24**; −15.6 (c=1.8).
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