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Total Synthesis of (+)-Breynolide

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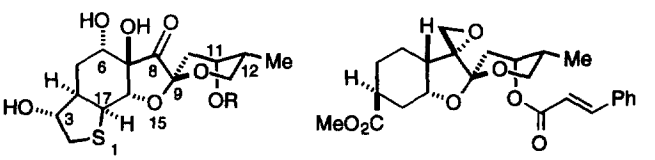
Abstract: The total synthesis of (+)-breynolide (**2**) is described. The primary focus is the synthesis of the advanced aldehyde intermediate **12**, which comprises the *cis*-fused perhydrobenzothiophene ring system. Three stereoselective cyclohexene epoxidation/epoxide opening sequences and a glycolate ester Claisen rearrangement, by which all of the necessary oxygen functionality in **12** is introduced before installation of the thioether, are employed.

Keywords: epoxides; oxygen heterocycles; rearrangements; sulfur heterocycles.

Breynins A and B are novel sulfur-containing glycosides which were isolated from the Taiwanese plant *Breynia officinalis* Hemsl[1] and have displayed significant oral hypocholesterolemic activity in rats.[2] Researchers at the Bristol-Banyu Research Institiute have characterized (+)-breynogenin (**1**) and (+)-breynolide (**2**) as the aglycon hydrolysis products of breynin A. The relative and absolute stereochemistry of (+)-breynolide was unambiguously determined by single crystal X-ray analysis.[1c]

Figure 1



Breynogenin (**1**) R=C(O)C_6H_4-*p*-OH Phyllanthocin (**3**)
Breynolide (**2**) R=H

We became interested in the breynins because of their pharmacological potential as well as their structural similarity to phyllanthocin (**3**), the aglycon nucleus of the phyllanthostatin antitumor agents.[3] These incentives have stimulated several synthetic investigations,[4] with total syntheses of **2** having been completed by Williams[4b] and Smith.[4c,d] Herein we report our efforts resulting in the enantioselective total synthesis of (+)-breynolide.

Our primary focus was the synthesis of aldehyde **12**, which comprises the *cis*-fused perhydrobenzothiophene ring system (Scheme I). Challenges inherent in **12** include six contiguous asymmetric centers, and the generally high oxidation level in the presence of an easily oxidizable thioether linkage. A strategy was thus adopted to introduce all of the necessary oxygen functionality contained in **12** *before* installation of the divalent sulfur atom. To this end, debromination of scalemic (*R*)-2-bromo-2-cyclohexen-1-ol (93% ee)[5] via metal/halogen exchange and protonation, followed by hydroxyl-directed epoxidation[6] and protection of the alcohol as the *m*-MPM ether gave the corresponding epoxide **4**. Eliminative epoxide opening using Noyori's procedure[7] gave the TBS-protected allylic alcohol **5**. Epoxidation of **5** with *m*-CPBA occurred predominantly from the less

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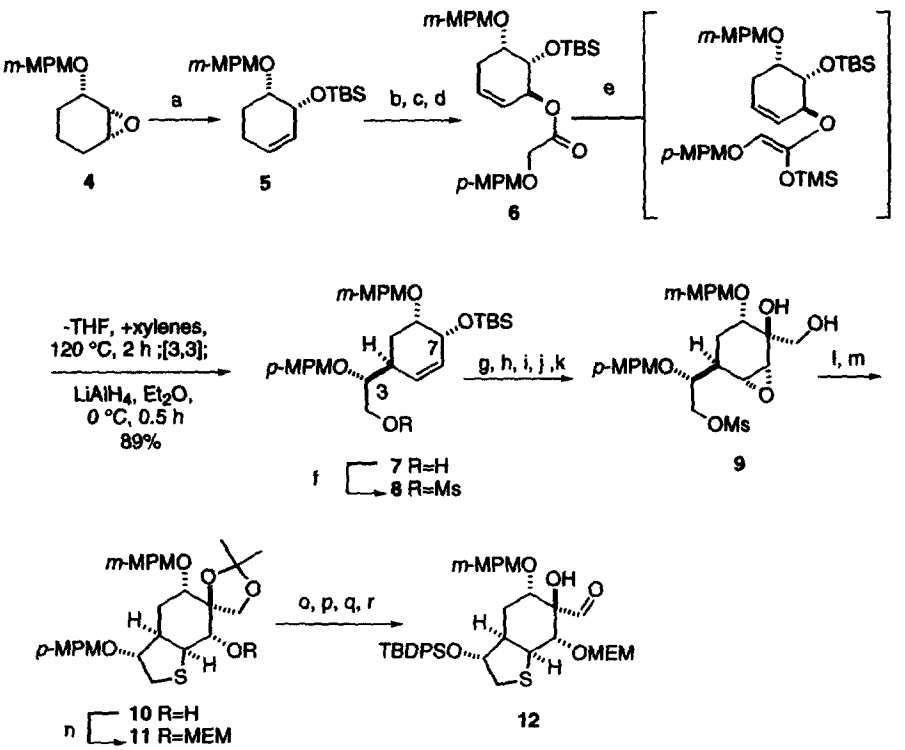
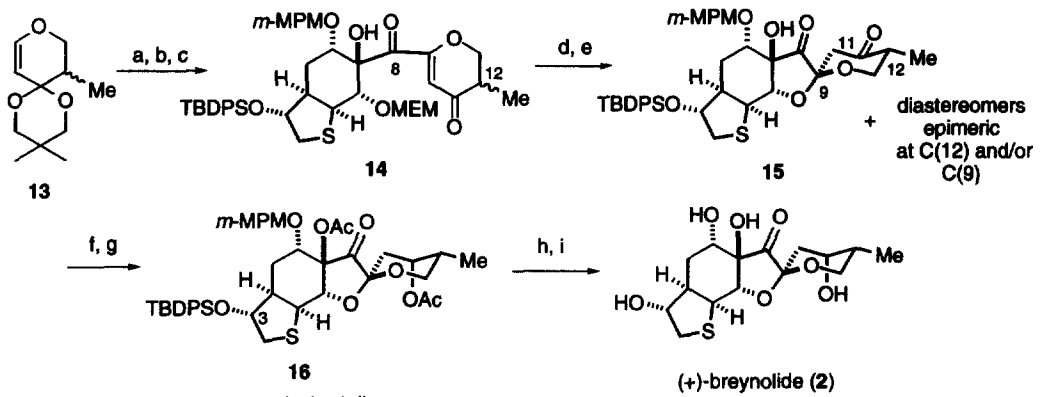
Scheme I



Reagents and conditions: (a) TBSOTf, 2,6-lutidine (5 eq), PhH, rt, 30 min; DBU (5 eq), rt, 10 h, 86%; (b) *m*-CPBA, PhH, 5 °C to rt, 92%; (c) TMSOTf, 2,6 lutidine (5 eq), PhH, rt, 30 min; DBU (5 eq), rt, 14 h; TBAF, 90%; (d) *p*-MPMOCH$_2$CO$_2$H, DIC, DMAP, THF, rt, 99%; (e) LHMDS, TMSCl:Et$_3$N (1:1, v/v), THF, -100 °C to rt; (f) MsCl, Et$_3$N CH$_2$Cl$_2$, -10 °C, 15 min, 96%; (g) HF•pyridine, THF, rt, 6 h, 91%; (h) *m*-CPBA, CH$_2$Cl$_2$, -10 °C to rt, 12 h, 92%; (i) Swern oxidation, 93%; (j) Ph$_3$P=CH$_2$, THF, 0 °C, 75%; (k) NMO, cat. OsO$_4$, acetone:H$_2$O (5:1), 76%; (l) 2,2-dimethoxypropane, PPTS, CH$_2$Cl$_2$, 98%; (m) Na$_2$S•9H$_2$O, EtOH, 60 °C, 2 h, 85%; (n) MEMCl, Hünig's base, DMAP, CH$_2$Cl$_2$, 16 h, 98%; (o) DDQ, CH$_2$Cl$_2$:H$_2$O (10:1), 20 min, 68%; (p) TBDPSCl, imidazole, CH$_2$Cl$_2$, 100%; (q) 80% AcOH (aq), 85%; (r) Swern oxidation, 95%.

hindered β-face of the alkene.[8] A second eliminative epoxide opening,[7] using TMSOTf, was followed by selective cleavage of the TMS ether and acylation to provide the protected glycolate ester **6**. Application of a chelation-controlled glycolate enolate Claisen rearrangement[9] provided primary alcohol **7** after direct reduction with LiAlH4. Highly stereoselective production of the correct stereochemistry at C(3) is rationalized by the enolate geometry and boat-like[10] rearrangement topology shown (brackets) . Mesylation of the primary alcohol provided **8**, and removal of the TBS protecting group followed by hydroxyl-directed[6] epoxidation of the alkene gave the corresponding α-epoxide as a single diastereomer. Swern oxidation[11] of the secondary alcohol at C(7), Wittig methylenation, and dihydroxylation of the resultant methylenecyclohexane intermediate under the Van Rheenen conditions[12] proceeded in a completely stereoselective manner from the less hindered β-face. Diol **9** was protected as the acetonide, and displacement of the primary mesylate with sulfide followed by intramolecular

Scheme II



Reagents and conditions: (a) *t*-BuLi, THF, -78 °C to 0 °C, 1.5 h; then aldehyde **12**, HMPA, THF, -78 °C to 0 °C; (b) oxalic acid (aq), CH_2Cl_2, rt, 2 h; (c) Swern oxidation, 54% for three steps from **12**; (d) wet $ZnBr_2$, CH_2Cl_2, rt, 16 h; (e) $TsOH{\bullet}H_2O$, benzene, rt, 48 h, 68% for two steps from **14**; (f) $LiBH(s\text{-}Bu)_3$, THF, -78 °C; (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 50% for two steps from **15**; (h) DDQ, CH_2Cl_2:H_2O (10:1), rt, 2 days, 88% based on recovered s.m.; (i) conc HCl (aq), MeOH, rt, 24 h, 100%.

epoxide opening[13] established the *cis*-fused tetrahydrothiophene ring system in **10**. Protection of the resultant secondary hydroxyl as the MEM ether[14] gave **11**. Completion of the synthesis of our left-piece coupling partner involved replacement of the potentially labile *p*-MPM group[15] with the more robust TBDPS group. This was followed by removal of the acetonide and Swern oxidation of the primary alcohol to give the α-hydroxy aldehyde **12**.

Coupling of **12** with Smith's C(9)-C(13) synthon **13**[4d] and elaboration to (+)-breynolide is shown in Scheme II. Lithiation[16] of racemic dihydropyran **13** and addition to **12** gave a mixture of four adducts diastereomeric at C(8) and C(12). Removal of the ketal protecting group and Swern oxidation of the C(8) secondary hydroxyl gave the pivotal enedione **14** as a 1:1 mixture of C(12) epimers. At this point, a thermodynamically driven spiroketalization/equilibration strategy, first employed by Smith,[4d] was used to preferentially obtain the correct stereochemical configurations at both C(9) and C(12). Removal of the MEM protecting group with wet $ZnBr_2$[14] followed by treatment of the crude product with *p*-toluenesulfonic acid in benzene at room temperature for 48 hours gave a mixture of diastereomeric spiroketals, including **15**.[17] Selective reduction of the less hindered C(11) carbonyl with lithium tri-*s*-butylborohydride afforded the C(11) axial alcohol.[18] This was followed by protection of the resultant C(7), C(11) diols as the acetates to facilitate chromatographic separation of **16** from the minor diastereomers. Finally, treatment of **16** with DDQ to remove the *m*-MPM protecting group,[19] followed by hydrolysis of the acetates and concomitant desilylation of the C(3) TBDPS ether with aqueous HCl in methanol, afforded synthetic (+)-breynolide (**2**), mp 240-242 °C (lit. mp 241-243 °C)[1b,4b], $[\alpha]_D^{25}$ +37.5° (c 0.20, MeOH).[20]

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References and Notes

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(15) Concern arose that the *p*-MPM ether (suitable for the glycolate Claisen rearrangement and tetrahydrothiophene construction) might not survive the upcoming spiroketalization reaction because of unpublished observations in our group of acid lability of *p*-MPM ethers. See also Kocienski, P. J. *Protecting Groups*; Thieme: 1994, p 52. This switch maintains the differential protection of the C(3), C(6) and C(11) secondary hydroxyls in **16**, necessary for elaboration to breynogenin and breynin A, which bears a trisaccharide glycosidic attachment at C(3).
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