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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. © 1998 Elsevier Science Ltd. All rights reserved.

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Breynias A and B are novel sulfur-containing glycosides which were isolated from the Taiwanese plant *Breynia officinalis* Hemsl<sup>1</sup> and have displayed significant oral hypocholesterolemic activity in rats.<sup>2</sup> Researchers at the Bristol-Banyu Research Institute 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.<sup>1c</sup>

Figure 1



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.<sup>3</sup> These incentives have stimulated several synthetic investigations,<sup>4</sup> with total syntheses of 2 having been completed by Williams<sup>4b</sup> and Smith.<sup>4c,d</sup> 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)<sup>5</sup> via metal/halogen exchange and protonation, followed by hydroxyl-directed epoxidation<sup>6</sup> and protection of the alcohol as the *m*-MPM ether gave the corresponding epoxide 4. Eliminative epoxide opening using Noyori's procedure<sup>7</sup> gave the TBS-protected allylic alcohol 5. Epoxidation of 5 with *m*-CPBA occurred predominantly from the less

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**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<sub>2</sub>CO<sub>2</sub>H, DIC, DMAP, THF, rt, 99%; (e) LHMDS, TMSCI:Et<sub>3</sub>N (1:1, v/v), THF, -100 °C to rt; (f) MsCI, Et<sub>3</sub>N CH<sub>2</sub>Cl<sub>2</sub>, -10 °C, 15 min, 96%; (g) HF•pyridine, THF, rt, 6 h, 91%; (h) *m*-CPBA, CH<sub>2</sub>Cl<sub>2</sub>, -10 °C to rt, 12 h, 92%; (i) Swern oxidation, 93%; (j) Ph<sub>3</sub>P=CH<sub>2</sub>, THF, 0 °C, 75%; (k) NMO, cat. OsO4, acetone:H<sub>2</sub>O (5:1), 76%; (l) 2,2-dimethoxypropane, PPTS, CH<sub>2</sub>Cl<sub>2</sub>, 98%; (m) Na<sub>2</sub>S•9H<sub>2</sub>O, EtOH, 60 °C, 2 h, 85%; (n) MEMCI, Hünig's base, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 16 h, 98%; (o) DDQ, CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O (10:1), 20 min, 68%; (p) TBDPSCI, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, 100%; (q) 80% AcOH (aq), 85%; (r) Swern oxidation, 95%.

hindered  $\beta$ -face of the alkene.<sup>8</sup> A second eliminative epoxide opening,<sup>7</sup> 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<sup>9</sup> 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<sup>10</sup> rearrangement topology shown (brackets). Mesylation of the primary alcohol provided 8, and removal of the TBS protecting group followed by hydroxyl-directed<sup>6</sup> epoxidation of the alkene gave the corresponding  $\alpha$ -epoxide as a single diastereomer. Swern oxidation<sup>11</sup> of the secondary alcohol at C(7), Wittig methylenation, and dihydroxylation of the resultant methylenecyclohexane intermediate under the Van Rheenen conditions<sup>12</sup> proceeded in a completely stereoselective manner from the less hindered  $\beta$ -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<sub>2</sub>Cl<sub>2</sub>, rt, 2 h; (c) Swern oxidation, 54% for three steps from 12; (d) wet ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 16 h; (e) TsOH•H<sub>2</sub>O, benzene, rt, 48 h, 68% for two steps from 14; (f) LiBH(*s*-Bu)<sub>3</sub>, THF, -78 °C; (g) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 50% for two steps from 15; (h) DDQ, CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O (10:1), rt, 2 days, 88% based on recovered s.m.; (i) conc HCI (aq), MeOH, rt, 24 h, 100%.

epoxide opening<sup>13</sup> established the *cis*-fused tetrahydrothiophene ring system in **10**. Protection of the resultant secondary hydroxyl as the MEM ether<sup>14</sup> gave **11**. Completion of the synthesis of our left-piece coupling partner involved replacement of the potentially labile *p*-MPM group<sup>15</sup> with the more robust TBDPS group. This was followed by removal of the acetonide and Swern oxidation of the primary alcohol to give the  $\alpha$ -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<sup>16</sup> 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,<sup>4d</sup> was used to preferentially obtain the correct stereochemical configurations at both C(9) and C(12). Removal of the MEM protecting group with wet ZnBr2<sup>14</sup> 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.<sup>17</sup> Selective reduction of the less hindered C(11) carbonyl with lithium tri-*s*-butylborohydride afforded the C(11) axial alcohol.<sup>18</sup> 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,<sup>19</sup> 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)<sup>1b,4b</sup>,  $[\alpha]_D^{25} + 37.5^{\circ}$  (c 0.20, MeOH).<sup>20</sup>

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## **References and Notes**

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