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A NOVEL APPROACH TO BREYNOLIDE

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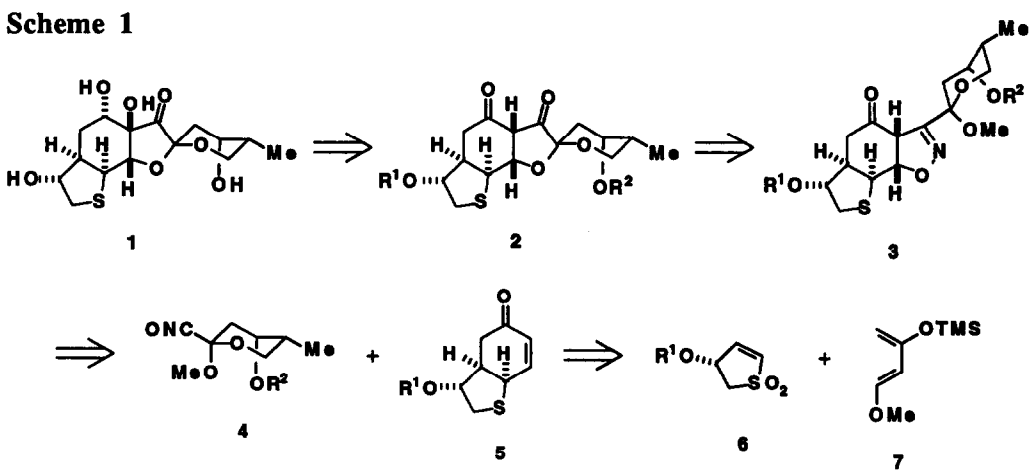
Abstract. The viability of the key steps in our approach to the novel sesquiterpene breynolide (**1**) has been verified by preparation of the hydrobenzothiophene **16**. The sequence features a Diels-Alder reaction of **10** with **7** to lead eventually to **13**; subsequent dipolar cycloaddition of **13** with a functionalized nitrile oxide gave **16**.

Breynolide (**1**) is the aglycone of the hypocholesterolemic agent breynin A, which was isolated from the Taiwanese plant *Breynia officinalis hems 1*.[1-3] The structure of **1** was originally established by X-ray crystallography.[4] The novelty of the structure of **1** coupled with its biological importance have stimulated several synthetic investigations,[5-7] and the total synthesis of **1** has been independently reported by Williams[6] and Smith.[7] More recently the structures of breynins A and B have been established.[8]

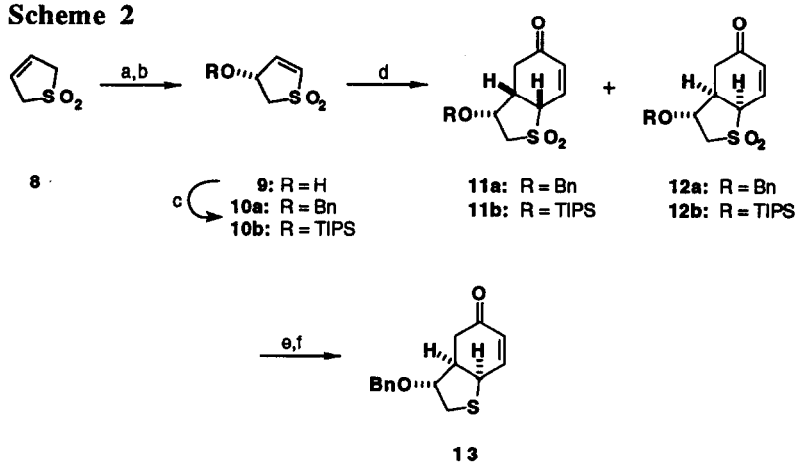
Our own interest in breynolide evolved from our synthesis of the structurally related sesquiterpene phyllanthocin, and the strategy that evolved for our approach to **1** (Scheme 1) was derived from that effort.[9] We reasoned that breynolide (**1**) should be accessible by refunctionalization of **2**, which, in close analogy with our previous work,[9,10] should be accessible by reduction of the oxazoline in **3** followed by acid-catalyzed transketalization of the intermediate hydroxy ketone. The most convergent approach to **3** was envisaged to involve dipolar cycloaddition of the nitrile oxide **4** with the unsaturated bicyclic ketone **5**,[11] which would be produced by the Diels-Alder reaction of the dienophile **6** with the Danishefsky diene **7**.[12] We now wish to describe initial experiments in this area that verify the underlying viability of this approach to **1**.

Scheme 1



The first problem that had to be addressed in the undertaking was the construction of a suitable derivative of a hydrobenzothiophene of the general type **5**. Although several possibilities may be envisioned, the one outlined in Scheme 2 emerged as one workable sequence. The allylic alcohol **9** was readily prepared by conversion of the inexpensive sulfolene **8** into the corresponding chlorohydrin, which is also commercially available, followed by dehydrochlorination.[13] The secondary hydroxyl group was protected as its benzyl or triisopropylsilyl ether, **10a** or **10b**, respectively. The dienophile **10a** was heated in a sealed tube with the diene **7** at 170-180 °C for 48 h, and the intermediate crude cycloadduct was then heated in benzene containing pyridinium *p*-toluenesulfonate (PPTS); this treatment resulted in desilylation with concomitant loss of methanol to give a mixture (1:1.2) of the cycloadducts **11a** and **12a** in 82% yield. Thinking that the cycloaddition might proceed with a higher level of diastereofacial selectivity, we also subjected the dienophile **10b** to the same sequence of reactions. Although this process was indeed more stereoselective, the improvement was not dramatic, and a mixture (1:2.5) of **11b** and **12b** was obtained. The regiochemical outcome of these cycloadditions could be readily ascertained upon analysis of their ^{1}H NMR spectra including COSY experiments, but it was not possible to unequivocally establish the facial selectivity by NMR owing to the complexity of the multiplets arising from the bridgehead protons. To resolve this issue, the structures of **11b**[14] and **12a**[15] were secured by X-ray analyses. The sulfone moiety of **12a** was reduced by treatment with DIBAL-H (60%, unoptimized),[16] and the mixture (6:1) of intermediate allylic alcohols was oxidized by a Swern oxidation[17] to give the dipolarophile **13** in 43% overall yield. The silyl protecting group on **12b** was not stable to the conditions required to reduce the sulfone, so even though the diastereoselectivity of the Diels-Alder reaction of **10b** was better than for **10a**, only the benzyl protected adduct was suited for further elaboration.

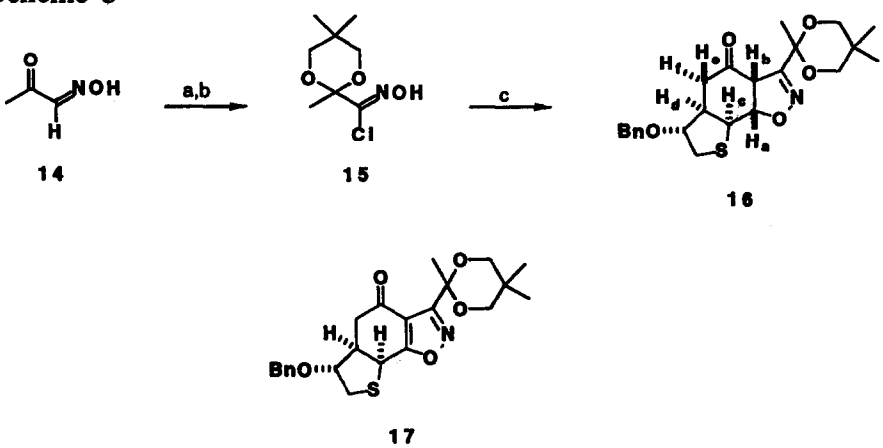
Scheme 2



(a) HOAc, H_2SO_4, H_2O, *tert*-BuOCl, rt, 24 h. (b) NH_3 (liq). (c) BnBr, NaH, *n*-Bu_4NI, THF, rt, 2 h or TIPS-Cl, Im-H, DMF, rt, 24 h. (d) **7**, mesitylene, reflux, 48 h; PPTS, benzene, reflux, 24 h. (e) DIBAL-H, CH_2Cl_2, reflux, 24 h. (f) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 1 h.

With the hydrobenzothiophene **13** in hand, the stage was set for the dipolar cycloaddition. Although use of the nitrile oxide **4** will offer a more convergent entry to intermediates that could be elaborated into **1**, we elected to examine first the regio- and stereoselectivity of the process in a simple model. Toward this end, the oxime **14** was converted into the hydroxamoyl chloride **15** by sequential ketalization and chlorination. The nitrile oxide derived from **15** was generated *in situ* in the presence of the enone **13** to furnish the cycloadduct **16** as the only characterizable product, albeit in modest yield. The regio- and stereochemical outcome of this cycloaddition were assigned based upon careful examination of the ^{1}H NMR of **16**.[18] Central to this conclusion was the appearance of a long range W-type coupling between H_b and H_e (J = 1.9 Hz) indicating that both protons are probably equatorial on the six-membered ring, which appears therefore to reside in a distorted chair conformation. Based upon this assumption and examination of molecular models, the observed coupling constant between H_a and H_c of 3.4 Hz suggests a trans relationship between H_a and H_c with a dihedral angle of about 110° rather than a cis relationship wherein the dihedral angle would be approximately 0-10°. The regiochemistry was confirmed by an X-ray analysis of the partially aromatized compound **17**, which was serendipitously obtained upon slow aerial oxidation of **16** that occurred upon prolonged standing.

Scheme 3



14 **15** **16** **17**

(a) TMS-Cl, 2,2-dimethylpropane-1,3-diol, CH_2Cl_2, rt, 36 h. (b) NCS, DMF, rt, 1.5 h. (c) **13**, Et_2O, Et_3N, rt, 56 h.

The successful preparation of **16** in this model study establishes the merit of our synthetic approach to breynolide (**1**) as outlined in Scheme 1. Work to extend these discoveries to the total synthesis of **1** are in progress, and the results of these investigations will be reported in due course.

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18. Partial ^{1}H NMR spectra **16:** δ 5.26 (dd, J = 3.4, 10.0 Hz, H_a), 4.18 (dd, J = 3.4, 5.6 Hz, H_c), 4.08 (dd, J = 1.9, 10.0 Hz, H_b), 2.73 (dd, J = 11.1, 15.1 Hz, H_f), 1.76 (ddd, J = 1.9, 2.8, 15.1, H_e).

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