ORGANIC LETTERS

2003
Vol. 5, No. 23
4441−4444

Synthesis of the Integrastatin Nucleus Using the Ramberg–Bäcklund Reaction

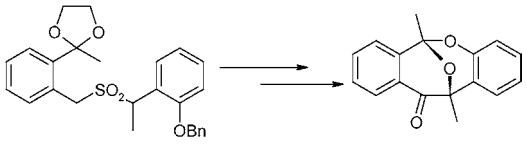
Jonathan S. Foot,[†] Gerard M. P. Giblin,[‡] and Richard J. K. Taylor*,[†]

Department of Chemistry, University of York, Heslington, York, YO10 5DD, UK, and Department of Medicinal Chemistry, Neurology and GI CEDD, GlaxoSmithKline, The Frythe, Welwyn, Herts AL6 9AR, UK

rjkt1@york.ac.uk

Received September 16, 2003

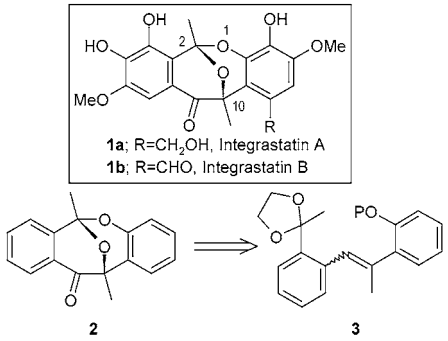
ABSTRACT



The first synthesis of the tetracyclic nucleus of the Integrastatins, natural products that have been shown to selectively inhibit HIV-1 integrase, is reported. Key steps of this synthesis involve a novel cis-selective Ramberg–Bäcklund reaction and an unusual Lewis acid-promoted cyclization step.

Integrastatin A (**1a**) and B (**1b**) (Scheme 1) are two recently discovered natural products isolated from both an unnamed fungal source (ATCC74478) and from an endophytic *Ascochtya* species (ATCC74477), which have been found to selectively inhibit the strand-transfer reaction of recombinant HIV-1 integrase at micromolar concentrations.[1] They are based on a novel [6.6.6.6] tetracycle, and although they contain two chiral centers, they exist in nature in racemic form ((*R*,*R*)-form shown).

Scheme 1. Integrastatins A & B and the Integrastatin Tetracyclic Nucleus, **2**



As part of our ongoing interest in the synthesis of highly oxygenated natural products,[2] it was decided to investigate the total synthesis of both Integrastatins. Given the novel structure of the tetracyclic nucleus **2**, we first explored synthetic approaches to this simplified analogue by functionalization of alkene **3**, obtained by retrosynthetic analysis (Scheme 1).

Failure of Wittig, Grignard, Julia, and lithiation chemistries to produce **3** led us to the Ramberg−Bäcklund reaction (RBR).[3]

To this end, the two coupling partners **6** and **7** (Scheme 2) were synthesized from the commercially available 2-methylacetophenone (**4**) and 2-hydroxyacetophenone (**5**). Coupling and oxidation of the resultant thioether proceeded smoothly to afford the sulfone **9** in 52% yield overall.

Sulfone **9** was then subjected to the in situ chlorination−Ramberg−Bäcklund reaction using the conditions described

[†] University of York.
[‡] GlaxoSmithKline.

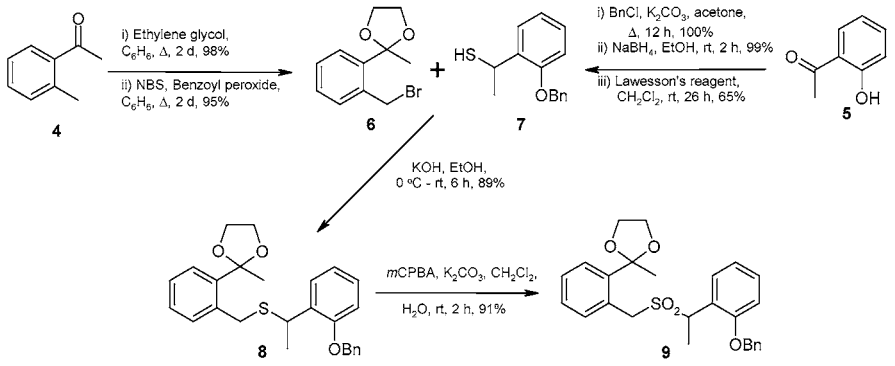
(1) Singh, S. B.; Fink. D. L.; Quamina, D. S.; Pelaez, F.; Teran, A.; Felock, P.; Hazuda, D. J. *Tetrahedron Lett.* **2002**, *43*, 2351.

(2) (a) Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7209. (b) Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Org. Biomol. Chem.* **2003**, *1*, 104. (c) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237. (d) Ragot, J. P.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1981. (e) Alcevaz, L.; MacDonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707 and references therein.

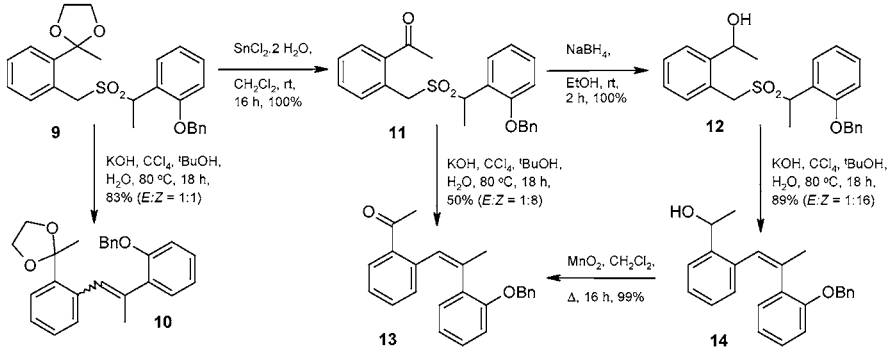
(3) (a) Ramberg, L.; Bäcklund, B. *Arkiv Kemi. Mineral. Geol.* **1940**, *27*, 13A. (b) Casy, G.; Taylor, R. J. K. *Org. React.* **2003**, *62*, 357.

10.1021/ol035786v CCC: $25.00 © 2003 American Chemical Society
Published on Web 10/11/2003

Scheme 2. Formation of the RBR Precursor



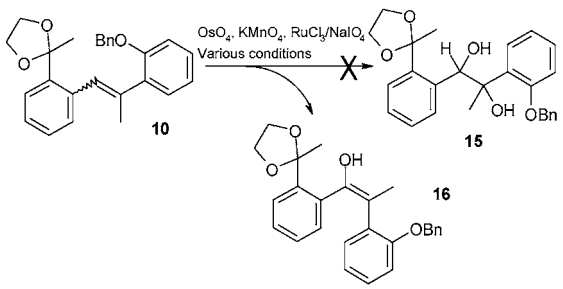
Scheme 3. Ramberg−Bäcklund Experiments



by Meyers et al. (Scheme 3),[4] to give the corresponding olefin **10** in 83% yield as a 1:1 *E*:*Z* mixture.[5] It was found, however, that both the free acetophenone **11** and the corresponding benzyl alcohol **12** also underwent the RBR, under the same conditions, to afford predominantly the cis-isomers of **13** (*E*:*Z* = 1:8, 50%) and **14** (*E*:*Z* = 1:16, 89%). In the literature, methyl stilbenes are normally formed with the trans-isomer predominating.[4,6] We are currently carrying out further studies to rationalize these unexpected results.

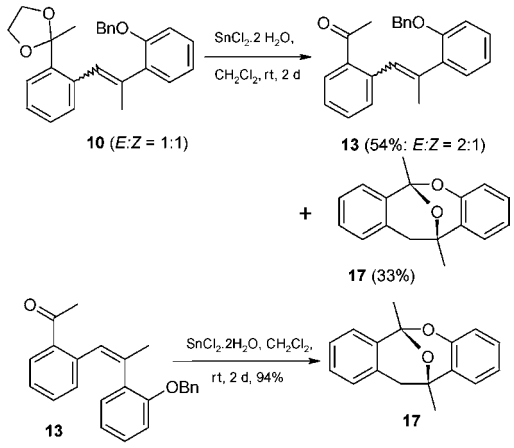
We next intended to dihydroxylate the newly formed double bond, by using osmium, ruthenium, or permanganate salts, but none gave the desired diol **15** (Scheme 4). Instead we observed either oxidatively cleaved products or the enol **16**, a result that led us to discontinue this approach.

Scheme 4. Attempted Dihydroxylation Experiments



Attempting to transform **10** into **13** through Lewis acid-promoted ketal removal,[7] we discovered that the tetracycle **17** was formed as a minor byproduct, along with the desired olefin **13** as a 2:1 mixture of *E*:*Z* isomers (Scheme 5).

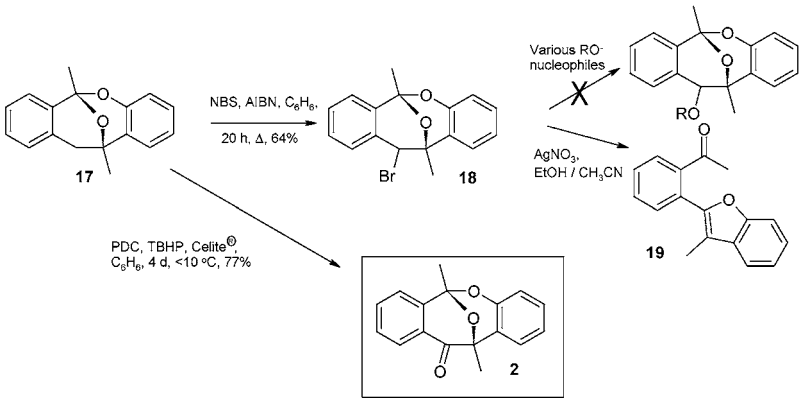
Scheme 5. Formation of the Deoxy-nucleus, **17**



As analysis of these results indicated that the (*Z*)-isomer underwent preferential cyclization, we then subjected a

(4) Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

Scheme 6. Bromide and Displacement Trials: Formation of the Integrastatin nucleus



sample of **13** obtained through RBR of **12** (*E*:*Z* = 1:16) to excess tin(II) chloride dihydrate, affording the tetracycle **17** in an excellent 94% yield (Scheme 5) as colorless crystals. The structure of **17** was confirmed by X-ray crystallography (Figure 1).[8]

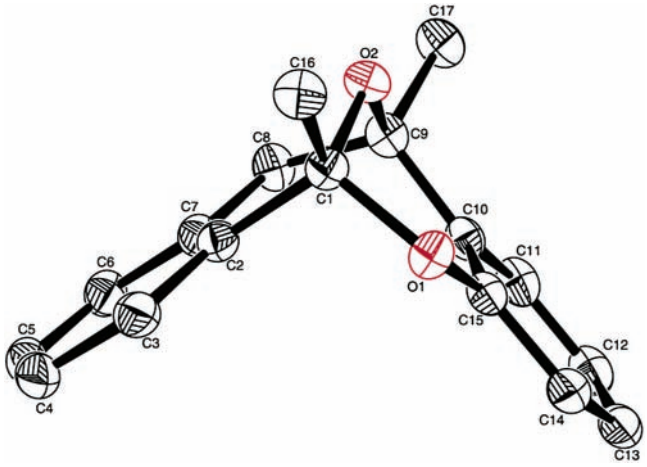


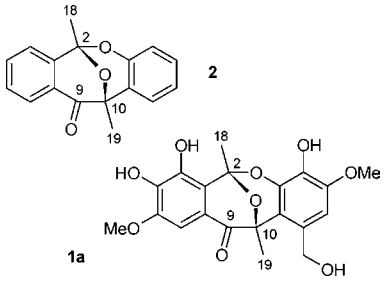
Figure 1. ORTEP drawing of tetracycle **17** (50% probability thermal ellipsoids).

We believe that the mechanism involves the initial loss of the benzyl protection group (as occasionally seen with Lewis acids[9]), followed by internal hemiacetal formation and cyclization onto the double bond. Since the reaction only appears to occur in the case of the cis-isomer, we deduce that the double bond is left intact until quite late in the mechanistic pathway. Further experiments are underway to evaluate this hypothesis.

Initial attempts at the benzylic oxidation of **17** (SeO_2, IBX, PCC, PDC, etc) were unsuccessful. Radical bromination, which gave **18**, was successful (see Scheme 6) but subsequent oxygen displacement reactions also failed. In the case of SN2-type conditions, no reaction at all was observed, while with SN1 reactions (using silver salts), the molecule underwent rapid intramolecular rearrangement to afford the novel benzofuran product **19**.

It was deduced that the bromide **18** was too hindered for displacement reactions. We therefore sought a direct radical-based oxidation process. Numerous reagents were investigated, but success was achieved using TBHP and PDC supported on Celite (Scheme 6).[10,11] We discovered that it was crucial to keep the temperature below 10 °C, and this produced a slow conversion. However, using this procedure, we observed the racemic integrastatin nucleus **2** in a 77%

Table 1. Comparison of Reported (Integrastatin A)[1] and Observed ^{13}C NMR Shifts



carbon	literature[1] δ_C (**1a**)/ppm[a]	observed δ_C (**2**)/ppm[a]
2	97.8	96.3
9	193.7	192.9
10	77.1	77.1
18	26.5	25.9
19	25.8	19.6

[a] Carried out in 1:1 $CDCl_3/CD_3CN$, 100 MHz.

(5) **Representative RBR Procedure.** To a stirred solution of sulfone in CCl_4 (5 mL/mmol), ^{t}BuOH (5 mL/mmol), and water (1 mL/mmol) was added powdered KOH (20 equiv standard, 40 equiv if free alcohol was present). The reaction was then heated at 80 °C until complete consumption of sulfone was observed by TLC analysis. The solvent was removed in vacuo and the residue extracted with EtOAc, washing with water and saturated NaCl solution, before drying over magnesium sulfate. Filtration and removal of solvent in vacuo, followed by purification (flash chromatography, eluting in petroleum ether/EtOAc) afforded the desired olefin.

(6) Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C. D. *J. Chem. Soc., Chem. Commun*. **1994**, 1771.

(7) Ford, K. L.; Roskamp, E. J. *Tetrahedron Lett*. **1992**, *33*, 1135.

(8) CCDC no. 219622.

yield (based on recovered starting material; actual yield 41%, with 47% unreacted starting tetracycle).

Full product analysis was in accordance with the proposed structure, while comparison of the carbon-13 NMR shifts (Table 1) provided convincing evidence that **2** is indeed the Integrastatin core.

(9) (a) Kadam, S. M.; Nayak, S. K.; Banerji, A. *Tetraedron Lett.* **1992**, *33*, 5129. (b) Park. M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett*. **1987**, *28*, 3823.

(10) Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem*. **1987**, *52*, 5048

(11) **Procedure for Oxidation of 17.** To a stirred solution of **17** (0.03 g, 0.12 mmol), PDC (0.26 g, 0.7 mmol), and Celite (0.2 g) in benzene (3.5 mL) at 6−10 °C under nitrogen was added TBHP (5.5 M in decane, 0.13 mL, 0.7 mmol). The reaction mixture was stirred below 10 °C for 4 days, with further addition of TBHP (2 × 0.13 mL) after 36 and 72 h. Filtration of the reaction through a pad of Celite, washing with EtOAc, and removal of solvent in vacuo, followed by purification (flash chromatography, eluting in 15:1 petroleum ether/EtOAc), afforded the integrastatin nucleus, **2** (0.013 g, 41%), and unreacted **17** (0.014 g, 47% recovered).

In summary, we have successfully synthesized the racemic core of the Integrastatins in 11 steps, with an overall yield of 33%, through application of a cis-selective Ramberg−Bäcklund reaction and a novel Lewis acid-promoted cyclization. We are currently investigating the extension of our route to the synthesis of the Integrastatin natural products.

Acknowledgment. We thank Dr. A. C. Whitwood for his help with X-ray crystallography and the E.P.S.R.C. and GSK for their financial support (J.S.F).

Supporting Information Available: Experimental procedures and full data for **14**, **17**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035786V