ORGANIC LETTERS

2001
Vol. 3, No. 2
279−281

Synthetic Studies toward Anisatin: A Formal Synthesis of (±)-8-Deoxyanisatin

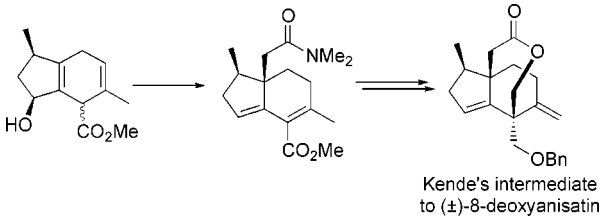
Teck-Peng Loh* and Qi-Ying Hu

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

chmlohtp@nus.edu.sg

Received November 23, 2000

ABSTRACT



An efficient strategy to construct the congested C-7a quaternary chiral center of anisatin was developed, by way of an Eschenmoser–Claisen rearrangement. Conversion of the resultant amide to Kende's ϵ-lactone intermediate 3 in four steps completed a concise formal synthesis of (±)-8-deoxyanisatin (2).

Anisatin (**1**), the convulsant principal of the seeds of Japanese star anise (*Illicium anisatum*, L.), was first isolated pure by Lane et al. in 1952[1] and fully characterized by Yamada's group in 1968.[2] The sesquiterpene toxin features a highly oxygenated indan backbone with eight contiguous chiral centers, among which four are adjacent quaternary carbons, the construction of which represents one of the most demanding tasks in multistep complex molecule synthesis.[3] Consequently, synthetic studies toward anisatin offer numerous opportunities for the development of new synthetic strategies to this end. We hereby present an efficient approach to forge the congested C-7a quaternary chiral center in a labile system, leading to a formal synthesis of (±)-8-deoxyanisatin (**2**, Figure 1).

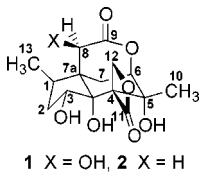


Figure 1.

In view of its intricate architecture and biological activity, anisatin has attracted extensive synthetic studies.[4] In 1982, the late Woodward's group disclosed an elegant intramolecular ene model study to construct the quaternary C-7a and vicinal C-8 chiral centers in one step.[4a] Unfortunately, ensuing application of this strategy to the synthesis of anisatin proved unsuccessful as far.[4b] Three years later, Kende and Chen reported the total synthesis of (±)-8-deoxyanisatin,[4c] but it was not until 1990, nearly forty years since its isolation, that Niwa et al. published the first total synthesis of anisatin in 39 steps.[4d] Both routes employed Robinson annulation to generate C-7a in an early stage of synthesis. The introduction of C-7a at a later stage offers an alternative concise avenue to the target, despite earlier futile attempts due to Woodward, inspiring us to carry out studies.

(1) Lane, J. F.; Koch, W. T.; Leeds, N. S.; Gorin, G. *J. Am. Chem. Soc.* **1952**, *74*, 3211.

(2) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199.

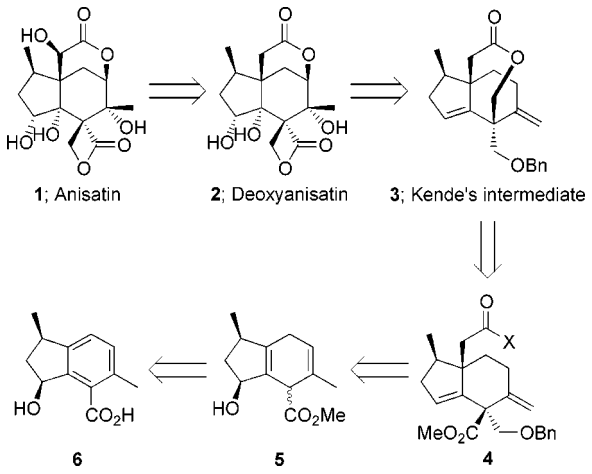
(3) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(4) (a) Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111. (b) Lindner, D. L. Ph.D. Thesis, Harvard University, Cambridge, MA, 1982. (c) Kende, A. S.; Chen, J. *J. Am. Chem. Soc.* **1985**, *107*, 7184. (d) Niwa, H.; Nisiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001. (e) Charonnat, J. A.; Nishimura, N.; Travers, B. W.; Waas, J. R. *Synlett* **1996**, 1162.

10.1021/ol006918c CCC: $20.00
Published on Web 12/28/2000

Our retrosynthetic analysis of anisatin is outlined in Scheme 1. The key step in our plan involves a [3,3]-Claisen

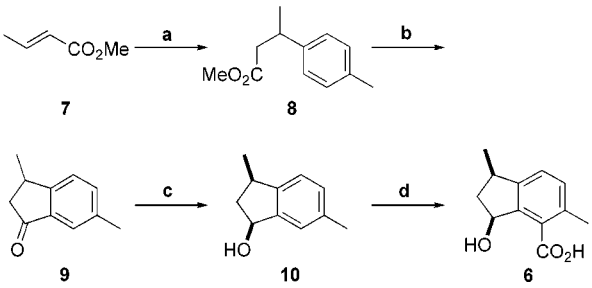
Scheme 1



rearrangement to construct the C-7a quaternary center in **4**. We envisaged that a few manipulations would convert **4** into ϵ-lactone **3**, which was a key intermediate in Kende's total synthesis of (±)-8-deoxyanisatin.

Our synthesis commences from the preparation of key intermediate carboxyindanol **6** (Scheme 2). Michael addition

Scheme 2[a]

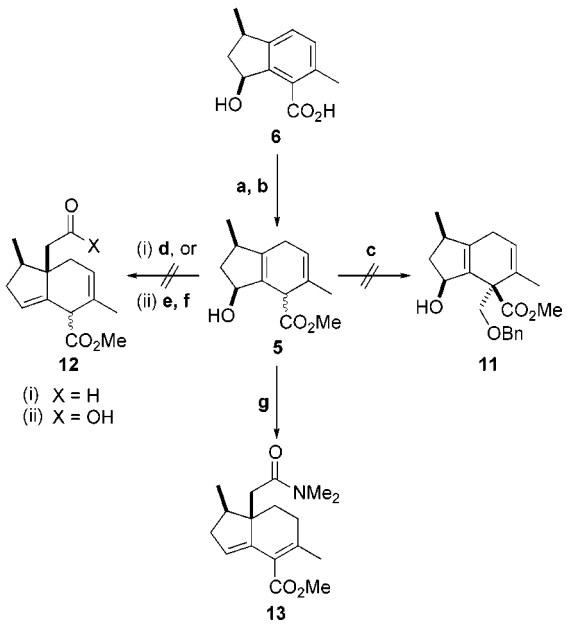


(a) *p*-TolMgBr, CuI (5 mol %), Et_2O, 0 °C, 3 h; (b) PPA, 90 °C, 48 h; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C, 2 h; (d) *n*-BuLi (4 equiv), TMEDA (4 equiv), hexane, reflux, 3 h, then CO_2, 0 °C, overnight, then 1 M HCl, 0 °C.

of *p*-TolMgBr to methyl crotonate (**7**) with a catalytic amount of CuI in ether at 0 °C afforded the methyl ester **8** in 80% yield, which underwent a smooth intramolecular Friedel−Crafts acylation[5] to indanone **9** in 93% yield. To reach carboxyindanol **6**, **9** was reduced under Luche[6] conditions at −78 °C to provide a 10:1 ratio of the required *syn* vs *anti* diastereomeric indanol **10** in 96% yield. Finally, carboxylation by means of directed *ortho* metalation[7] gave the desired key intermediate **6** in 65% yield, amounting to 42% total yield over four steps.

At this junction, we moved into the second phase of synthesis entailing the introduction of quaternary chiral center C-7a (Scheme 3). To this end, 1,4-diene **5** was obtained via

Scheme 3[a]



(a) Na, NH_3, reflux, 1 h, then NH_4Cl; (b) CH_2N_2, Et_2O, 0 °C; (c) LDA, THF, −78 °C, then $BnOCH_2Cl$, to 0 °C; (d) $Hg(OAc)_2$, CH_2═CHOEt, reflux; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C; (f) LiHMDS, THF, −78 °C, then TMSCl, to 25 °C; (g) $CH_3C(OMe)_2$-NMe_2 (5 equiv), xylene, reflux, 48 h.

Birch reduction[7d,8] of **6**, followed by esterification with CH_2N_2 in 60% yield. It is suspected that cyclohexa-1,4-diene **5** will be susceptible to re-aromatization[8,9] or isomerization to the corresponding 1,3-diene. To prevent these, attempts were made to alkylate C-4 which nevertheless failed due to the facile re-aromatization[10] of **5** under basic conditions. For this reason, our attention turned to implementation of the [3,3]-Claisen rearrangement protocol to construct C-7a instead.[3,11] A vinyl ether Claisen rearrangement[12] was first

(5) Corey, E. J.; Behforouz, M.; Ishiguro, M. *J. Am. Chem. Soc.* **1979**, *101*, 1608.

(6) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(7) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Panetta, C. A.; Dixit, A. S. *Synthesis* **1981**, 59. (c) Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1304. (d) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031.

(8) (a) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep.* **1986**, *3*, 35. (b) Schultz, A. G. *J. Chem. Soc., Chem. Commun.* **1999**, 1263. (c) Rabideau, P. W.; Marcinow, Z. In *Organic Reactions*; Paquette, L. A. ed.; Wiley: New York, 1992; Vol. 42, Chapter 1.

(9) (a) Plieninger, H.; Ege, G. *Angew. Chem.* **1958**, *70*, 505. (b) Hendry, D. G.; Schuetzle, D. *J. Am. Chem. Soc.* **1975**, *97*, 7123.

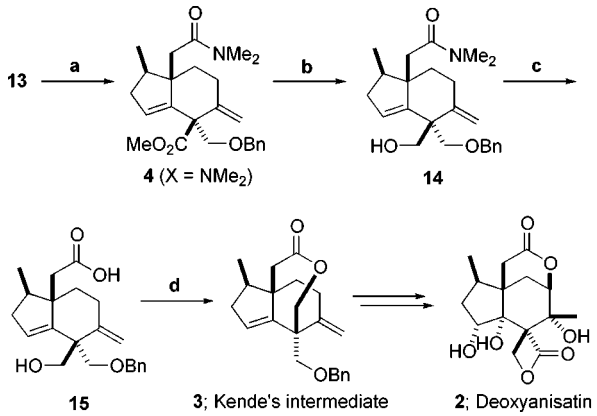
(10) Baker, A. J.; Goudie, A. C. *J. Chem. Soc., Chem. Commun.* **1972**, 925.

(11) For recent review, see: (a) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17. For examples, see: (b) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330. (c) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc.* **1981**, *103*, 2446. (d) Deng, W.; Jensen, M. S.; Overman, L. E.; Rucker, P. V.; Vionnet, J.-P. *J. Org. Chem.* **1996**, *61*, 6760. (e) Nussbaumer, C.; Fráter, G.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1016.

explored, but only an unidentified tarry product was obtained. Ensuing investigation with Ireland−Claisen rearrangement also resulted in re-aromatized products.[11,13] These failures hinted at the lability of **5**, which posed additional challenges to our synthesis. Fortunately, subsequent experimentation with Eschenmoser−Claisen rearrangement[14] succeeded in the generation of quaternary C-7a, providing amide **13** in 50% yield. The *syn* relative stereochemistry at C-1 and C-7a in **13** was established by NOESY.

The successful preparation of **13** marked the entry into the next synthetic phase, that is the synthesis of Kende's ϵ-lactone key intermediate **3** (Scheme 4). First, a selective

Scheme 4[a]



(a) LDA, cyclohexane/THF, −78 °C, then $BnOCH_2Cl$, to 25 °C, 1 h; (b) $LiBH_4$, THF, 25 °C, 48 h; (c) KOH, ethylene glycol, sealed tube, 200 °C, 12 h; (d) *p*-TsOH, toluene, 70 °C, 0.5 h.

alkylation at C-4, in the presence of several other potential alkylation sites, was required. Under optimal conditions (LDA, cyclohexane/THF, −78 °C), the desired alkylation product **4** was obtained predominantly in 40% yield, which underwent selective reduction of the ester functionality to provide **14** in 50% yield. The amide in **14** was next hydrolyzed by heating with KOH in ethylene glycol at 200 °C under sealed tube conditions to afford carboxylic acid **15**. Finally, mild lactonization to ϵ-lactone **3** was effected by heating with catalytic amount of *p*-TsOH in toluene at 70 °C in 70% yield over two steps. The structure of **3** was proved by comprehensive 2D NMR studies (COSY, NOESY, HMQC, and HMBC), and the proton NMR is substantially identical to that of Kende and Chen.[15]

In summary, an efficient strategy for the construction of sterically congested quaternary chiral centers in labile system has been developed by means of an Eschenmoser−Claisen rearrangement after a Birch reduction, in the course of pursuing the total synthesis of anisatin. This strategy was realized in the successful generation of the C-7a quaternary chiral center, leading to a concise formal synthesis of (±)-8-deoxyanisatin. The synthesis of Kende's ϵ-lactone intermediate **3** was accomplished in 11 steps from readily available starting materials. Further synthetic studies toward anisatin are currently in progress.

Acknowledgment. We are indebted to Professor Kende of the University of Rochester for kindly forwarding to us a copy of the data for ϵ-lactone **3** and his helpful discussion. We gratefully acknowledge the National University of Singapore for generous financial support. We also wish to thank Madam Han Yan-Hui for high-field NMR (500 MHz) assistance.

Supporting Information Available: Complete experimental details, including characterization data for all new compounds, and copies of COSY, NOESY, HMQC, and HMBC NMR spectra of ϵ-lactone **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006918C

(12) Burghstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198.
(13) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
(14) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. (b) Kanematsu, K.; Nishizaki, A.; Shiro, S. M. *Tetrahedron Lett.* **1992**, *33*, 4967.
(15) Personal communications with Professor A. S. Kende from the University of Rochester.