ORGANIC LETTERS

2003
Vol. 5, No. 25
4911−4913

Synthesis of the Polycyclic Ring Systems of Artocarpol A and D

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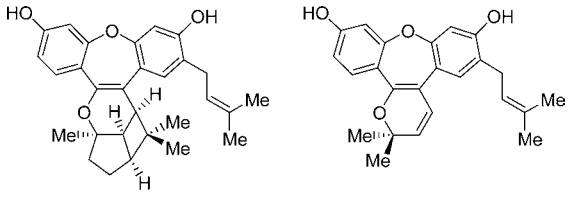
Received October 23, 2003

ABSTRACT



The first synthesis of the polycyclic ring systems of artocarpol A and D has been accomplished. These natural products were isolated recently from the root bark of *Artocarpus rigida*, and artocarpol A has been shown to have potent antiinflammatory properties. The synthesis of an artocarpol D analogue was achieved on condensation of 11*H*-dibenzo[*b*,*f*]oxepin-10-one with senecialdehyde. The reaction of this oxepinone with citral afforded a 2*H*-pyran that on subsequent irradiation afforded an analogue of artocarpol A.

Recently, the isolation and structural characterization of a series of novel phenolic compounds from the root bark of *Artocarpus rigida* have been reported.[1−2] Artocarpol A **1** and D **2** share a highly functionalized dibenzo[*b*,*f*]oxepin ring system and represent intriguing targets for total synthesis (Figure 1). In addition, artocarpol A **1** and other members

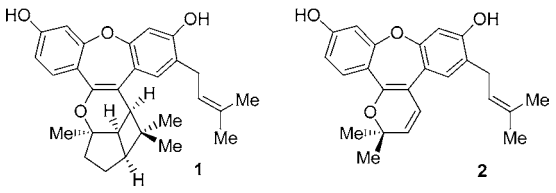


Figure 1. Artocarpol A **1** (relative stereochemistry) and artocarpol D **2**.

of this expanding family of natural products have notable antiinflammatory properties.[1] In this Letter, we report the first study toward the total synthesis of these natural products that has resulted in the development of an efficient and novel means to elaborate their complete polycyclic ring systems.

Retrosynthetic analysis of artocarpol A **1** indicated that it could be prepared from the 2*H*-pyran **3** via an intramolecular photochemical [2 + 2] cycloaddition reaction (Figure 2). The

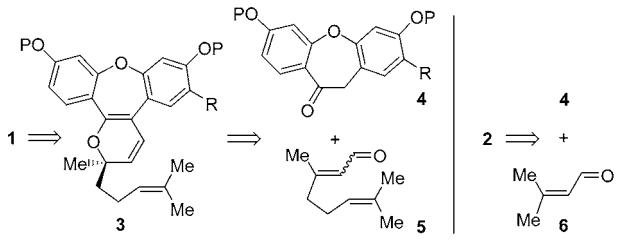


Figure 2. Retrosynthetic analysis of artocarpol A **1** and artocarpol D **2**.

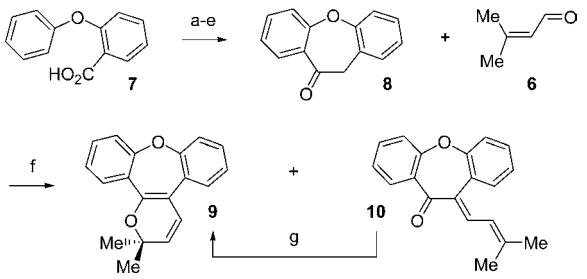
stereochemistry of this cycloaddition reaction would be controlled by the single stereogenic center of the 2*H*-pyran. The latter compound could in principle be prepared from the functionalized oxepinone **4** (R = prenyl) on condensation with citral **5** following an electrocyclic ring-closure reaction.[3] Subsequent deprotection of the phenol moieties would then complete the synthesis of this complex polycyclic natural

10.1021/ol0360703 CCC: $25.00
Published on Web 11/08/2003

product in a particularly direct manner. Alternately, the oxepinone **4** (R = Br or H) could be employed so that the prenyl substituent could be installed at a later stage in the synthesis.[4] This latter strategy could alleviate potential complications in the proposed photochemical reaction. In a similar fashion, the polycyclic ring system of artocarpol D **2** could be established in a single laboratory operation from the functionalized oxepinone **4** (R = prenyl) on condensation with senecialdehyde **6**. The total synthesis of artocarpol D **2** would then be completed on deprotection of the phenol moieties.

To demonstrate the feasibility of the proposed condensation reaction, the known oxepinone **8** was prepared as a model substrate in five steps from commercially available 2-phenoxybenzoic acid **7** by adaptation of literature procedures (Scheme 1).[5] A variety of basic, acidic, and Lewis

Scheme 1. Synthesis of Artocarpol D Analogue (**10**)[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 4 h, 90%; (b) $SOCl_2$, pyridine, PhH, reflux, 24 h, 98%; (c) NaCN, DMSO, rt, 24 h, 90%; (d) KOH, EtOH, H_2O, reflux, 4 h, 85%; (e) polyphosphoric acid, 100 °C, 4 h, 84%; (f) allylamine (6 equiv), $MgSO_4$, THF, reflux, 8 h, 40% (**9**), 26% ((*E*)-**10**); (g) allylamine (3 equiv), $MgSO_4$, THF, reflux, 8 h, 80%.

acidic reagents were screened in order to identify suitable reaction conditions to effect the condensation reaction of oxepinone **8** and senecialdehyde **6**.[6] It was found that the use of primary amines specifically caused complete reaction of the oxepinone **8** to occur and resulted in the direct formation of the artocarpol D analogue **9**. In addition, the unsaturated ketone (*E*)-**10** was isolated as a single double-bond isomer. The geometry of this double bond was determined by NMR experiments (NOESY) that showed an absence of contacts between the olefinic and aromatic protons of concern. The corresponding (*Z*)-double-bond isomer of the unsaturated ketone **10** was not isolated as it presumably undergoes a concomitant cyclization reaction to afford the desired target compound. The optimized reaction conditions involved heating a mixture of the oxepinone **8** with senecialdehyde **6** (6 equiv) and allylamine (6 equiv) in THF for 8 h. The addition of anhydrous magnesium sulfate to the reaction mixture caused a slight improvement in the yield of the reaction products but did not affect the rate of the reaction. The chromatographically isolated unsaturated ketone **10** was smoothly interconverted under similar reaction conditions to afford the artocarpol D analogue **9** in a combined overall yield of 61%.

The reaction of the oxepinone **8** with citral **5** (*E*:*Z* ≈ 2:1) under the optimized reaction conditions described above afforded a chromatographically separable mixture of the known self-condensation product of citral **11**,[7] the cross-condensation products (*E*,*E*)-**12** and (*E*,*Z*)-**13**, and the desired 2*H*-pyran **14** (Scheme 2). The corresponding isomers (*Z*,*E*)-**12** and (*Z*,*Z*)-**13** of the cross-condensation products were not isolated, as again these strained compounds presumably spontaneously cyclized to afford the 2*H*-pyran. The cross-condensation products **12** and **13** were subsequently recycled to afford the 2*H*-pyran **14** in a combined overall yield of 70%.

Irradiation of a dilute deoxygenated solution of the 2*H*-pyran **14** and benzophenone in benzene with a high-pressure mercury lamp within a quartz reaction flask afforded the artocarpol A analogue **15** in 45% yield.[8] The starting material **14** was also recovered (15%), as well as a mixture of the unsaturated ketones (*E*,*E*)-**12** and (*E*,*Z*)-**13** (10%). The latter compounds are presumably formed, in this instance, via the photochemical ring-opening reaction of the 2*H*-pyran **14**. The structure of the artocarpol A analogue **15** was fully assigned on the basis of a series of multidimensional NMR experi-

(1) (a) Chung, M.-I.; Ko, H.-H.; Yen, M.-H.; Lin, C.-N.; Yang, S.-Z.; Tsao, L.-T.; Wang, J.-P. *Helv. Chim. Acta* **2000**, *83*, 1200. (b) Ko, H.-H.; Lin, C.-N.; Yang, S.-Z. *Helv. Chim. Acta* **2000**, *83*, 3000. (c) Ko, H.-H.; Yang, S.-Z.; Lin, C.-N. *Tetrahedron Lett.* **2001**, *42*, 5269. (d) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J. P. *Helv. Chim. Acta* **2002**, *85*, 1626. (e) Lu, Y.-H.; Lin, C.-N.; Ko, H.-H.; Yang, S.-Z.; Tsao, L.-T.; Wang, J. P. *Helv. Chim. Acta* **2003**, *86*, 2566.

(2) For other natural products previously isolated from *Artocarpus rigida*, see: (a) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1990**, *31*, 2173. (b) Hano, Y.; Inami, R.; Nomura, T. *Heterocycles* **1993**, *35*, 1341.

(3) To the best of our knowledge, there is no direct precedent for this transformation in which a cyclic or acyclic ketone is condensed with an α,β-unsaturated aldehyde to afford a 2*H*-pyran. However, the formation of 2*H*-pyrans from 1,3-dicarbonyl compounds and α,β-unsaturated aldehydes via the Knoevenagel condensation reaction is well established; see: (a) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Heathcock, C. H., Vol. Ed.; Pergamon Press: Oxford, 1992; Vol. 2, p 341. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729 and references therein.

(4) Hoarau, C.; Pettus, T. R. R. *Synlett* **2003**, 127.

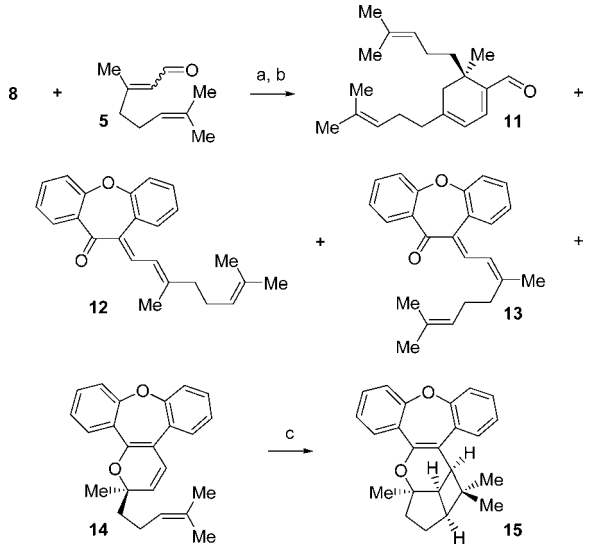
(5) (a) Manske, R. H. F.; Ledingham, A. E. *J. Am. Chem. Soc.* **1950**, *72*, 4797. (b) Atkinson, D. C.; Godfrey, K. E.; Meek, B.; Saville, J. F.; Stillings, M. R. *J. Med. Chem.* **1983**, *26*, 1353. (c) Yoshioka, M.; Osawa, H.; Fukuzawa, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 877. (d) Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer, H. M., III; Kruse, H. *J. Med. Chem.* **1980**, *23*, 494. (e) Harris, T. W.; Smith, H. E.; Mobley, P. L.; Manier, D. H.; Sulser, F. *J. Med. Chem.* **1982**, *25*, 855.

(6) For example, deprotonation of the oxepinone **8** at −78 °C with lithium diisopropyl amide and subsequent reaction with senecialdehyde **6**, on stirring for 8 days at room temperature, led to the slow formation of the 2*H*-pyran **9** (23%) and the unsaturated ketone **10** (20%). Similar results were obtained when citral **5** was employed as the electrophilic reaction component. The low yield is due to competitive deprotonation of these enolizable aldehydes by the lithium enolate of the oxepinone. This conclusion is supported by the fact that on repeating the reaction with β-phenylcinnamaldehyde, the corresponding unsaturated ketone was isolated as the sole reaction product in good yield (80%). Interestingly, this reaction product did not undergo cyclization to form the corresponding 2*H*-pyran.

(7) Holst, P. B.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Bock, K. *Acta Chem. Scand.* **1994**, *48*, 765.

(8) For related intramolecular photochemical [2 + 2] cycloaddition reactions of 2*H*-chromenes, see for example: (a) Crombie, L.; Ponsford, R. *Tetrahedron Lett.* **1968**, 5771. (b) Yamaguchi, S.; Shouji, N.; Kuroda, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 305. (c) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559. (d) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

Scheme 2. Synthesis of Artocarpol A Analogue (**15**)[a]



[a] Reagents and conditions: (a) allylamine (6 equiv), $MgSO_4$, THF, reflux, 8 h, 20% (**11**), 27% ((*E*,*E*)-**12**:(*E*,*Z*)-**13** = 1:1.6), 50% (**14**); (b) (*E*,*E*)-**12**, (*E*,*Z*)-**13**, allylamine (3 equiv), $MgSO_4$, THF, reflux, 8 h, 80%; (c) benzophenone, PhH, *hν*, 24 h, 45% (**15**), 10% ((*E*,*E*)-**12**:(*E*,*Z*)-**13** = 1:1).

ments (COSY, HETCOR, and NOESY). The latter technique was used to assign the relative stereochemistry of the reaction product based on contacts between the bridgehead methyl and hydrogen substituents.[8]

The direct formation of the artocarpol D analogue **9** and the 2*H*-pyran **14** constitutes a novel reaction process.[3] We have considered that the mechanism of this reaction involves the reaction of the enol form of the oxepinone with the corresponding imines of the α,β-unsaturated aldehydes (Figure 3).[9−10] Subsequent elimination of the amine and cyclization of the resultant unsaturated ketones would lead to the formation of observed reaction products. This conclusion is based on the observation that under the reaction conditions employed, allylamine reacted rapidly with the aldehyde reaction components to form the corresponding imines. No reaction between allylamine and the oxepinone

(9) The proposed structure of artocarpol E has been reported as the enol form of a functionalized oxepinone (ref 1b).

(10) The enol of the oxepinone **8** would be expected to have a nonplanar structure; see: (a) Drake, J. A. G.; Jones, D. W. *Acta Crystallogr*. **1982**, *B38*, 200. (b) Shukla, D.; Wan, P. *J. Am. Chem. Soc.* **1993**, *115*, 2990.

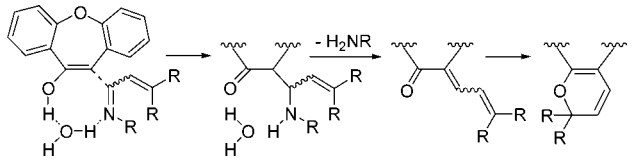


Figure 3. Proposed mechanism for the formation of the 2*H*-pyrans.

8 was observed. It has been reported that particularly forcing conditions ($TiCl_4$, PhH, reflux) are required in order to form the corresponding enamines of this oxepinone.[5e] It was also observed that the reaction of oxepinone **8** with the preformed and purified imine of allylamine and citral **5** (6 equiv), on heating at reflux in dry THF for 5 days, afforded the 2*H*-pyran **14** (40%) and a mixture of the unsaturated ketones (*E*,*E*)-**12** and (*E*,*Z*)-**13** (1.8:1, 19%). Similar results were obtained on repeating this reaction with the corresponding imine of allylamine and senecialdehyde **6**. Of note, the reactions were considerably slower under these anhydrous reaction conditions. However, the addition of a trace amount of water and magnesium sulfate decreased the amount of time required for these reactions to go to completion to ∼8 h. These latter observations have led us to tentatively conclude that a water molecule is involved in the reaction between the enol form of the oxepinone and the corresponding imines of the α,β-unsaturated aldehydes.

In conclusion, the polycyclic ring systems of artocarpol A **1** and D **2** have been elaborated in a direct and efficient manner from the known oxepinone **8**, citral **5**, and senecialdehyde **6**. Current work involves the synthesis and elaboration of the oxepinone **4** (R = H and Br; P = Me) in order to complete the total synthesis of artocarpol A **1** and D **2**.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and Simon Fraser University for financial support. M.P.P. thanks Simon Fraser University for a graduate research fellowship and entrance scholarships.

Supporting Information Available: Detailed experimental procedures and product characterization data for all of the compounds synthesized, as well as ^1H and ^{13}C NMR spectra for compounds **9**, **10**, and **12**−**15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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