J|A|C|S
COMMUNICATIONS

Published on Web 07/27/2002

Total Synthesis and Absolute Stereochemistry of Plakortone D

Patricia Y. Hayes and William Kitching*

Department of Chemistry, The University of Queensland, Brisbane 4072, Australia

Received April 30, 2002

Sponges of the genus *Plakortis* are prolific in their production of biologically active secondary metabolites, and peroxides and lactones are especially favored.[1] A particularly interesting group of such compounds comprises the plakortones A−F[2−5] (Figure 1) from the Caribbean sponges, *Plakortis halichondrioides* and *P. simplex*.

Plakortones A−D[2] constitute a new class of activators of cardiac SR-Ca^{2+}-pumping ATPase, and are relevant to correction of cardiac relaxation irregularities.[2] Plakortone D is the most active in this respect. Plakortones B−F[3] exhibit in vitro cytotoxic activity on a murine fibrosarcoma cell line, so that overall, the plakortones represent a new family of drugs of substantial pharmacological interest. The structures were deduced by NMR methods, and nOe difference data provided the relative stereochemistry portrayed in Figure 1; however, that at C10 was undetermined. The absolute

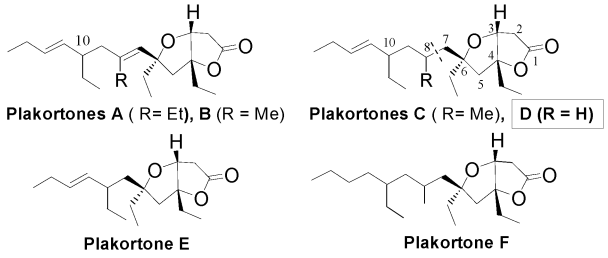
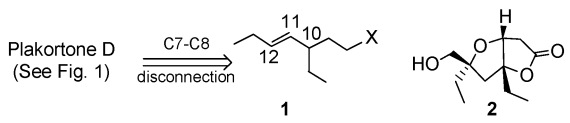


Figure 1.

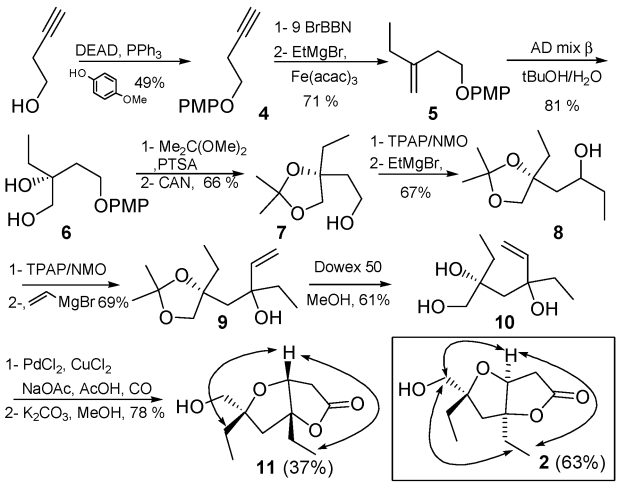
stereochemistry in the series was unknown. We now report the total synthesis of plakortone D,[6] which not only clarifies uncertain structural and stereochemical features but also enables acquisition of other plakortones and analogues, in the correct stereochemical series.

The constant structural motif in the plakortone series is the 2,6-dioxabicyclo[3.3.0]octan-3-one moiety, incorporating quaternary centers at C4 and C6 (numbering as in Figure 1, following the system of Patil[2]). We have demonstrated[6a] that these sterically congested bicyclic lactones are efficiently accessed by a palladium-(II)-mediated-hydroxy-cyclization−carbonylation−lactonization cascade,[7] so that the key disconnection in our approach to plakortone D was scission at C7−C8. This provides, along with the lactone **2**, the side chain unit **1** (C8−C14), that requires control at C10 and eventually an E-double bond (C11−C12).

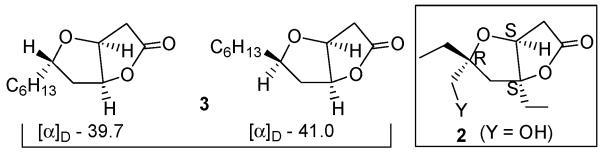


The plakortones A−F are all levorotatory.[2,3] Presuming that the bicyclic lactone moiety is the dominant contributor to the molecular

Scheme 1



rotation and recognizing that in a simpler lactone series,[7c] levo-enantiomers **3** manifest the sense of chirality shown, our initial quest was for the system **2**.



For the side chain unit **1** (C8−C14), we felt it prudent to acquire both C10 enantiomers for linkage to **2**, although there was an indication that one was more likely.[8]

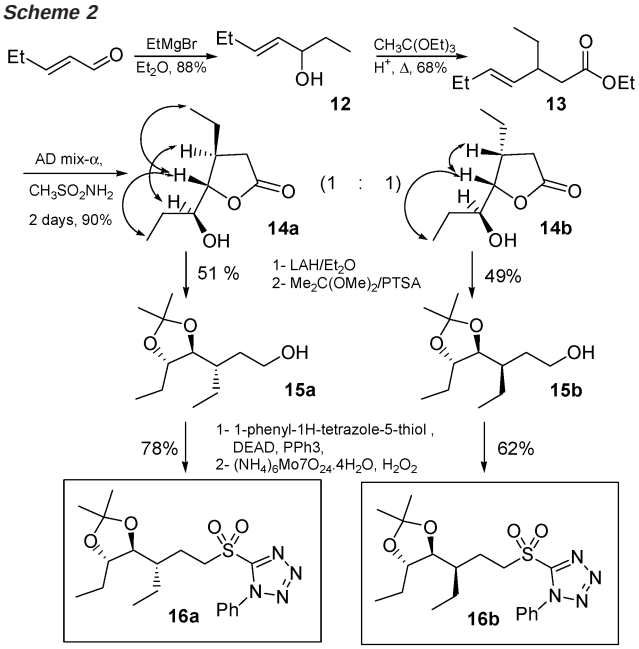
Synthesis of the Bicyclic Lactone 2. Inexpensive 3-butyn-1-ol was protected and converted to alkene **5**, the substrate for asymmetric dihydroxylation. Reaction with AD mix-β provided diol **6** of >95% ee (Mosher's ester) and predicted[9] **6** to be (*R*)-configured. This was confirmed by its levo-rotation.[10] Deprotection, oxidation, and addition steps provided sensitive triol **10** as a mixture of diastereomers. This was subjected to the Pd(II)-mediated lactone-forming cascade,[7c] which provided readily separated **11** and the required **2** (absolute stereochemistry determined by NOESY experiment of the benzyl derivatives of **2** and **11**, see Supporting Information)[6a] (Scheme 1).

Synthesis of the (C8−C14) Side Chain, 16a,b. γ,δ-Unsaturated ester **13** resulting from the Johnson variant of the enolate Claisen rearrangement,[11] with AD mix-α, provided in excellent yield (90%) a mixture of only two lactones, **14a** and **14b**.[12] NOESY spectra and X-ray crystal structure of the *p*-nitrobenzoate of **14b** established their relative stereochemistry, and on the basis of the Sharpless mnemonic and optical rotation data,[13] their absolute stereochemistry is as shown. Reduction of **14b** provided a triol, which as the acetonide **15b** was converted to the modified sulfone **16b**[14] ready

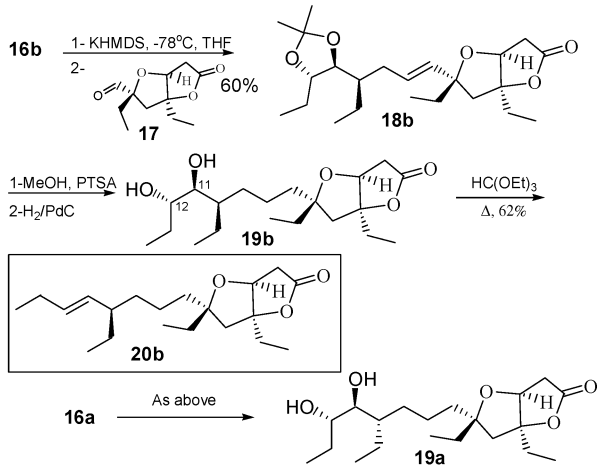
* To whom correspondence should be addressed. E-mail: Kitching@chemistry.uq.edu.au.

10.1021/ja026728s CCC: $22.00

Scheme 2



Scheme 3



for coupling. Similar processing of the lactone **14a** provided the epimeric sulfone **16a** (Scheme 2).

Lactone Side-Chain Coupling. Hydroxymethyl lactone **2** was oxidized (TPAP/NMO) to aldehyde **17**, (Scheme 3) which was immediately coupled with the anion of the sulfone **16b** to afford the elongated lactone **18b**. Acetonide removal and hydrogenation afforded the key diol **19b**. Most conveniently, Patil and co-workers[2] had treated (natural) plakortone D with both AD mix-α and AD mix-β to generate the 11,12-diols, with $[\alpha]_D$ of −27.3 and −9.8, and assigned as the α (*R*,*R*)- and β (*S*,*S*)-diols, respectively. However, correct application of the Sharpless mnemonic[9] requires a reversal of these assignments, so that the AD mix-α-derived diol with $[\alpha]_D$ −27.3 is (*S*,*S*)-configured. Our diol **19b** exhibited $[\alpha]_D$ −26.3, in good agreement.

Sulfone diol **16a**, epimeric at C10, was similarly coupled with the same lactone system **2**, to afford diol **19a**, $[\alpha]_D$ −25.5 (*c*, 0.27, $CHCl_3$). The ^{13}C NMR spectrum of the natural plakortone-D-derived (*S*,*S*)-diol (from AD mix α) matched with high precision the data for our synthesized diol **19b** but less well with the data for epimeric diol **19a**.[15] Consequently, the C10-ethyl-bearing center in plakortone D is (*R*)-configured, consistent with the result for the peroxide, plakortin.[8]

Finally, creation of the C11−C12 E-double bond requires stereospecific syn removal of the 1,2-diol unit. Reaction of **19b** with triethylorthoformate[16] afforded an ortho compound which was isolated in crude form and then heated at ∼180 °C for 1 h to provide cleanly the alkene **20b**. The ^1H and ^{13}C NMR and mass spectra of **20b** matched those of authentic plakortone D. The specific rotations were also in good agreement. Therefore plakortone D has structure **20b**.[17]

This work confirms the structure and absolute stereochemistry of plakortone D and almost certainly for this entire series of biosynthetically related lactones. Adaptation of the described route will provide other plakortones and analogues. This work will be reported at a later date.

Acknowledgment. We are grateful to the Australian Research Council for support and to Drs. Patil and Freyer (GlaxoSmithKline) for kindly providing copies of spectra of authentic plakortone D and the derived C11,12 diols. We thank Dr. P. Bernhardt for the X-ray structure of the *p*-nitrobenzoate of **14b**.

Supporting Information Available: Full experimental details for **18a,b**, **19a,b**, and **20b**, spectral data for compounds **2**, **6**−**9**, **11**, **14a,b**, **16a,b**, **18a,b**, **19a,b**, and **20b** and copies of the ^1H and ^{13}C spectra for **7**−**9**, **14a,b**, **18a,b**, **19a,b**, and **20b**, NOESY spectra for the benzyl derivatives of **2** and **11**, and crystal structure (ORTEP figure) of the *p*-nitrobenzoate derivative of **14b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) See for example Stierle, D. B.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 3396.
(2) Patil, A. D.; Freyer, A. J.; Bean, M. F.; Carte, B. K.; Westley, J. W.; Johnson, R. K.; Lahouratate, P. *Tetrahedron* **1996**, *52*, 377.
(3) Caffierei, F.; Fattorusso, E.; Taglialatela-Scafati, O.; Di Rosa, M.; Ianaro, A. *Tetrahedron* **1999**, *55*, 13831.
(4) Caffierei, F.; Fattorusso, E.; Taglialatela-Scafati, O.; Ianaro, A. *Tetrahedron* **1999**, *53*, 7045.
(5) Gochfeld, D. J.; Hamann, M. T. *J. Nat. Prod.* **2001**, *64*(11), 1477.
(6) For reported substructure syntheses, approaches, or comments, see: (a) Paddon-Jones, G. P.; Hungerford, N. L.; Hayes, P.; Kitching W. *Org. Lett.* **1999**, *1*, 1905. (b) Bittner, C.; Burgo, A.; Murphy, P. J.; Sung, C. H.; Thornhill, A. J. *Tetrahedron Lett.* **1999**, *40*, 3455. (c) Semmelhack, M. F.; Shaunnugam, P. *Tetrahedron Lett.* **2000**, *41*, 3567. (d) Hui, C. W.; Lee, M. K.; Wong, H. N. C. *Tetrahedron Lett.* **2002**, *43*, 123.
(7) (a) Semmelhack, M. F.; Bodurow, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (b) Gracza, T.; Hasenöhvl, J.; Stahl, V.; Jäger, V. *Synthesis* **1991**, 1108. (c) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; König, W.; Kitching, W. *J. Org. Chem.* **2001**, *66*, 7487 and reference therein.
(8) Degradation of plakortin[1,4] and application of NMR methods for determination of absolute stereochemistry indicated that C8 in this peroxide metabolite was likely to be (*R*)-configured. C8 in plakortin has likely nexus with C10 in plakortone D.
(9) Kold, H. C.; VanNievwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(10) The 2-methyl (lower) homologue of **6**, of known absolute stereochemistry (see: Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc*, **1995**, *117*, 10805) has $[\alpha]_D$ −7.7 (*c*, 2.8, $CHCl_3$), compared with $[\alpha]_D$ −9.3 (*c*, 1.0, $CHCl_3$) for **6**.
(11) Our original approach was based on initial kinetic resolution (asymmetric epoxidation) of the allylic alcohol **12** prior to the Claisen rearrangement. Paddon-Jones, G. C. Ph.D. Thesis, The University of Queensland, 1998, 160.
(12) See: Wang, Z.-M.; Zhang, X.-L, Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 6407.
(13) For **14a** and **14b**, $[\alpha]_D$ + 38.6 and + 20.3, respectively. (*S*,*S*)-lactones of this type are dextrorotatory.[12]
(14) Blakemore, P. R.; Cole, W. J.; Kocieñski, P. J.; Morley, A. *Synlett* **1998**, 26.
(15) As anticipated, the most significant differences in the ^{13}C chemical shifts occurred in the immediate structural vicinity of C10, as **19a** and **19b** are epimeric at this position.
(16) Crank, G.; Eastwood, F. W. *Aust. J. Chem.* **1964**, *17*, 1392.
(17) (Lit. $[\alpha]_D$ −26.3 (*c*, 1.27, $CHCl_3$))[2]. Measured $[\alpha]_D$ −24.5 (*c*, 0.2, $CHCl_3$). Pr. J. Boukouvalas (Laval University) has presented a synthesis of plakortone D (see abstract OE9, 38th IUPAC Congress Frontiers in Chemistry, Word Chemistry Congress 2001, Brisbane).

JA026728S