J|A|C|S
COMMUNICATIONS

Published on Web 02/16/2002

The Total Synthesis of (±)-Merrilactone A

Vladimir B. Birman and Samuel J. Danishefsky*

Department of Chemistry, Columbia University, Havemeyer Hall, New York, New York 10027, and Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021

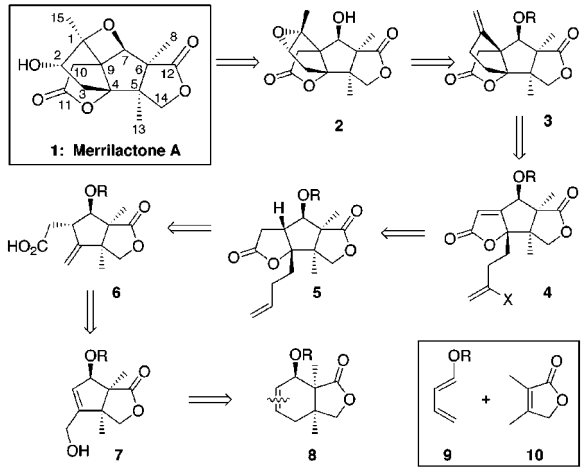
Received November 7, 2001

Neurotrophic factors are functionally defined as molecules which promote the maintenance and growth of neurons in vitro and in vivo.[1] Among such factors are the nerve growth factor (NGF) and glial cell-derived neurotrophic factor (GDNF). Intraventricular administration of NGF to rats and primates reduces cholinergic neuronal degeneration, with potential implications for the treatment of Alzheimer's disease.[2a,3] GDNF may have consequences in the treatment of Parkinson's disease.[2b] However, optimism along these lines is tempered by concerns as to the pharmacokinetics and bioavailability of polypeptidal factors.[3] It is in this connection that the discovery of nonpeptidal small molecules with neurotrophic properties is potentially of great significance.[4] It seems appropriate to explore nonpeptidal neurotrophic agents in detail as to their biological function and their usefulness, if any, in the treatment of neurodegenerative diseases. We felt that gaining a mastery of the total synthesis of such small-molecule natural products could be most helpful, not only in improving access to these difficultly available agents, but also in providing the basis for probing their SAR profiles.

Below, we describe the total synthesis of the pentacyclic sesquiterpene dilactone, merrilactone A (**1**). This compound had been obtained in 0.004% yield from the methanol extract of the pericarps of *Illicium merrillianum*.[5] Preliminary studies indicated that **1** greatly promotes neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1−10 μmol. Further investigations have been hampered by the scarcity of the natural merrilactone A.

Needless to say, the challenge of creating the densely oxygenated, highly compact architecture of merrilactone A in the laboratory added to the attractiveness of the project. One of the provocative features of the target system is the presence of an oxetane linkage bridging the β-faces of C7 and C1. We envisioned the possibility that such an oxetane might arise by Payne-like rearrangement of α-epoxide **2**. It was further conjectured that isomerization of exo-olefin **3** followed by epoxidation would lead to **2**. A critical step en route to **3** might be a free radical cyclization[6] of a substrate of type **4**, enabling formation of a new quaternary center in a densely substituted environment. It was further anticipated that suitable 2-fold oxidation of **5** might provide the required complementary functionality of **4**. This line of reasoning invited a proposal that overall "allyl-lactonization" could be used to convert **6** to **5**. Recognition of the γ,δ-unsaturated acid character of **6** called to mind the possibility of reaching this intermediate by Claisen rearrangement via **7**. Preparation of **7** was to be achieved through a ring cleavage−reclosure sequence from **8**. The latter structure, in turn, was suggestive of a Diels−Alder-based construction. However, the prospects of a direct cycloaddition between **9** and **10** to reach **8** were not promising. Even uncongested butenolides are not particularly powerful dienophiles. The presence of the two methyl groups, creating a tetrasubstituted "dienophilic" double bond, was likely to preclude such a cycloaddition. Hence, we sought to

Scheme 1



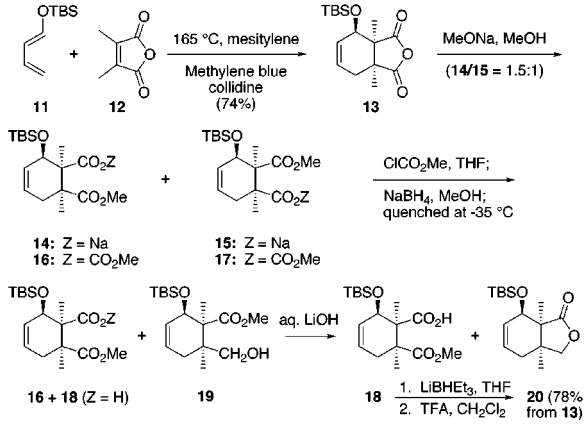
compensate for the expected steric impediment through recourse to a more reactive dienophile substructure (cf. **12**). The development of a scheme which, in effect, circumvents the inertness of **10** was a key challenge to our prospectus (Scheme 1).

Happily, reaction of 2,3-dimethylmaleic anhydride (**12**)[7] and **11**[8] occurred under the conditions shown, to afford **13** in 74% yield. We next turned to regioselective reduction of the C14 carbonyl group (future merrilactone A numbering). In the event, attempted reductions with conventional borohydride reagents led to complex mixtures. This lack of selectivity necessitated a somewhat awkward, but high-yielding, circumvention. It was established that ring opening of **13** with sodium methoxide proceeded smoothly. Treatment of the resulting salts (**14** and **15**) with $ClCO_2Me$ in THF afforded mixed anhydrides **16** and **17**. Remarkably, exposure of this mixture to the action of $NaBH_4$ and methanol[9] led to clean reduction of **17** while leaving **16** unchanged. Subsequent addition of lithium hydroxide to the mixture afforded compounds **18** and **20**, easily separable by a simple extraction. Treatment of **18** with $LiBHEt_3$[10] also afforded **20**. The regioconvergence of this scheme obviated any need for chromatographic separation of intermediates and afforded **20** in 78% overall yield from **13** (Scheme 2).

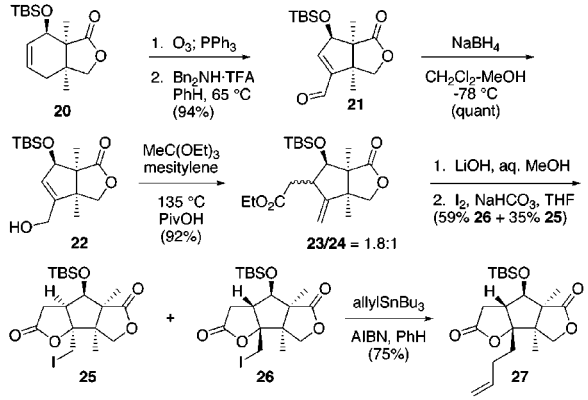
The stage was now set for the ring cleavage−reclosure sequence (cf. **8** → **7** in retrosynthesis plan). Ozonolysis of **20** followed by reductive workup, as shown in Scheme 3, led to a dialdehyde, which on aldol condensation using Corey's conditions[11a] afforded the cyclodehydrated product **21** in high yield.[11b] Following reduction[12] of the aldehyde function, allylic alcohol **22** was in hand. The next stage called for Claisen rearrangement to reach **23**. The most advantageous way to achieve this result proved to be via the Johnson ortho ester protocol.[13] The mixture of esters (**23**/**24** ∼1.8:1) thus produced was hydrolyzed, and the resultant acids subjected to iodolactonization. Two crystalline and chromatographically separable iodolactones, **25** and **26**, were obtained in 35 and 59% yields,

10.1021/ja012495d CCC: $22.00

Scheme 2



Scheme 3



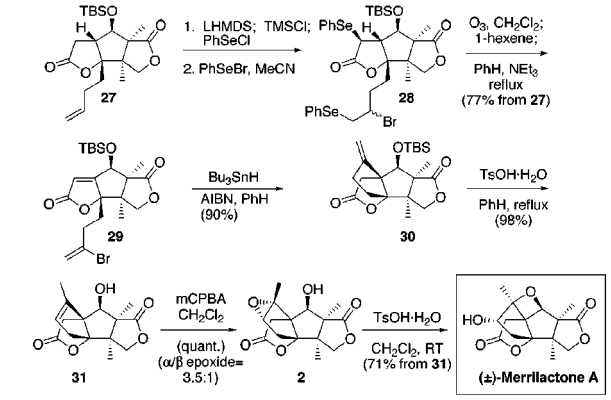
respectively. Chain extension of the required "anti-backbone" isomer **26** was accomplished (75% yield) by the elegant C-allylation method of Keck.[14]

As noted above, (cf. **5** → **4** in the retrosynthesis) oxidation at two sites would be required to complete the setting for the proposed key cyclization step (cf. **4** → **3**). An efficient sequence to deal with potentially awkward functional group management issues in advancing beyond **27** was developed. Thus, selenenylation at C10 was accomplished via an intermediate silyl ketene acetal. With this subgoal achieved, bromoselenenylation of the terminal vinyl group of **27** was conducted according to methodology introduced some years ago by Rauscher.[15] Concurrent oxidative deselenation afforded the desired **29**. The setting for testing the key free radical cyclization was at hand. Our initial concerns that the steric congestion at the sp^2 center at C9 might lead to the competitive reduction of the vinylic radical, fortunately, proved groundless. In the event, treatment of **29** under the standard conditions[6a] afforded a 90% yield of **30**.

Isomerization of the exo methylene group in **30** envisioned at the planning stage was accomplished concurrently with liberation of the C7 β-alcohol. While hydroxyl groups have often been used to direct epoxidation with peracids in a *syn* sense,[16] in the case at hand the congested nature of the β-face of the C1−C2 double bond is such that epoxidation occurs primarily (3.5:1) from its α-face (see compound **2**).[18] In the final step of the synthesis, merrilactone A is produced by an acid-induced homo-Payne rearrangement (see **2** → **1**). The spectroscopic properties of **31**, **2**, and **1** were in complete accord with the published data.[5b,17] Further confirmation came from the identity of the NMR spectra of synthetic (±)-**1** with those of natural merrilactone A (Scheme 4).[18]

In summary, a total synthesis of merrilactone A has been accomplished. Clearly, the synthesis leaves several issues of

Scheme 4



selectivity unsolved. These will be addressed either by optimization of the current scheme or via substantial reconfiguration of the synthetic strategy. However, we emphasize that even the first-generation route described above provides, for the first time, ample material for extensive preclinical evaluations of merrilactone A. Indeed, we are confident that the chemistry developed to date (20 steps, 10.7% overall yield) is amenable to scale-up to multigram levels. Moreover, the use of dimethylmaleic anhydride (**12**) as a dienophile leading to the incorporation of two angular methyl groups has broad potential implications which warrant follow-up.

Acknowledgment. This work was supported by the National Institutes of Health (Grant HL 25848). V.B.B. gratefully acknowledges the NIH for a postdoctoral fellowship (1 F32 NS 41726-01).

Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hefti, F. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 239.
(2) (a) Siegel, G. J.; Chauhan, N. B. *Brain Res. Rev.* **2000**, *33*, 199. (b) Gash, D. M.; Zhang, Z.; Ovadia, A.; Cass, W. A.; Yi, A.; Simmerman, L.; Russel, D.; Martin, D.; Lapchak, P. A.; Collins, F.; Hoffer, B. J.; Gerhardt, G. A. *Nature* **1996**, *380*, 252.
(3) Backman, C.; Rose, G. M.; Hoffer, B. J.; Henry, M. A.; Bartus, R. T.; Friden, P.; Granholm, A. C. *J. Neurosci.* **1996**, *16*, 5437.
(4) For a discussion of small molecule mimetics and for references to neurotrophic natural products, see: ref 1, pp 255−257.
(5) (a) Huang, J.-m.; Yokoyama, R.; Yang, C.-s.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111 (b) Huang, J.-m.; Yang, C.-s.; Tanaka, M.; Fukuyama, Y. *Tetrahedron* **2001**, *57*, 4691.
(6) (a) Marinovic, N. N.; Ramanathan, H. *Tetrahedron Lett.* **1983,** *24*, 1871. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
(7) DMMA itself is capable of reacting only with the most reactive dienes: (a) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893 and references therein. (b) Rae, I. D.; Serelis, A. K.; *Aust. J. Chem.* **1990**, *43*, 1941. (c) von Ziegler, K.; Flaig, W.; Velling, G. *Liebigs Ann.* **1950**, *567*, 204.
(8) Defoin, A.; Pires, J.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 1665.
(9) (a) Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* **1987**, 647. (b) Alexandre, F.-R.; Legoupy, S.; Huet, F. *Tetrahedron* **2000**, *56*, 3921.
(10) Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190.
(11) (a) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031. (b) No C7-epimerized material was detected.
(12) Ward, D. E.; Rhee, C. K. *Can. J. Chem.* **1989**, *67*, 1210.
(13) (a) Johnson, W. S.; Wertheman, L.; Bartlett, W. R.; Lee, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
(14) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.
(15) (a) Rauscher, S. *Tetrahedron Lett.* **1977**, *44*, 3909.
(16) Henbest, H. B.; Wilson, R. A. L. *Chem. Ind. (London)* **1956**, 659.
(17) While this work was in progress, a report by Fukuyama et al.[5b] appeared which described conversion of a closely related natural product, anislactone B, into merrilactone A proceeding via the same intermediates (**31** and **2**). Their procedure, with minor modifications, was utilized for the last two steps of this synthesis.
(18) We thank Professor Y. Fukuyama (Tokushima Bunri University) for providing us with the ^{1}H and ^{13}C NMR spectra of merrilactone A.

JA012495D