ORGANIC LETTERS

2006
Vol. 8, No. 21
4771−4774

Total Synthesis of Topopyrones B and D

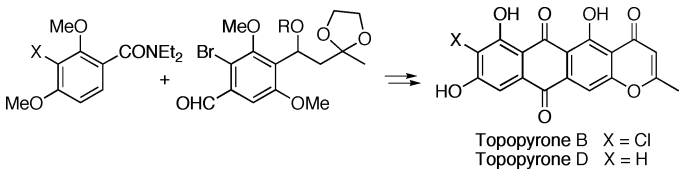
Jason Samuel Tan and Marco A. Ciufolini*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1, Canada

ciufi@chem.ubc.ca

Received July 14, 2006

ABSTRACT



We describe a straightforward synthesis of topopyrones B and D, which are potent and selective inhibitors of topoisomerase I. The chemistry should be suitable for additional structure–activity relationship (SAR) work.

Topoisomerases I and II (topo-I and topo-II) are nuclear enzymes that relax superhelical tension in DNA during replication, transcription, and repair events.[1] These enzymes operate by reversibly breaking one (topo-I) or both (topo-II) DNA strands and by unwinding the severed strand(s), thereby avoiding buildup of torsional energy. Interestingly, cancerous cells tend to overexpress topoisomerases, inhibition of which is fatal to the cell. Consequently, topoisomerase inhibitors have emerged as important antineoplastic agents.[2]

A number of antitumor drugs target topo-II.[3] Selective intervention at the level of topo-I constitutes an equally desirable strategy in cancer therapy. The prototype of all selective topo-I inhibitors is camptothecin,[4] derivatives of which are currently marketed for the treatment of various neoplastic conditions. Other natural products that behave as selective topo-I poisons include the fungal metabolite, hypoxyxylerone,[5] certain marine alkaloids,[6] and a family of recently discovered substances, which have been christened the "topopyrones" (Figure 1).[7] These compounds are based on an anthraquinone framework that carries an angularly (topopyrones A, **1**, and C, **2**) or linearly (topopyrones B, **3**, and D, **4**) fused γ-pyrone ring. Bioactivity is especially pronounced in topopyrone B, the potency of which toward topo-I is comparable to that of camptothecin.[8]

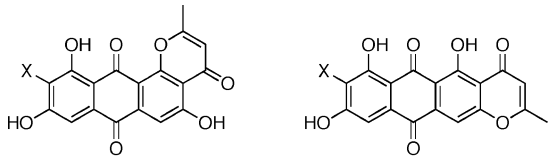


Figure 1. Structures of topopyrones A−D.

To our knowledge, no synthetic work toward **1**−**4** has been detailed in the peer-reviewed literature as of this writing,

(1) Recent review: Champoux, J. J. *Annu. Rev. Biochem.* **2001**, *70*, 369.
(2) Denny, W. A. *Expert Opin. Emerging Drugs* **2004**, *9*, 105. (b) *Advances in Pharmacology*; Liu, L. F., Ed.; Academic Press: San Diego, CA, 1994; Vol. 29B.
(3) Recent review: Kellner, U.; Sehested, M.; Jensen, P. B.; Gieseler, F.; Rudolph, P. *Lancet Oncol.* **2002**, *3*, 235.
(4) Reviews: (a) Rothenberg, M. L. *Ann. Oncol.* **1997**, *8*, 837. (b) Versace, R. W. *Expert Opin. Ther. Pat.* **2003**, *13*, 1.
(5) Isolation: (a) Edwards, R. L.; Fawcett, V.; Maitland, D. J.; Nettleton, R.; Shields, L.; Whalley, A. J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 1009. Bioactivity: (b) Gimbert, Y.; Chevenier, E.; Greene, A. E.; Massardier, C.; Piettre, A. EP 01 402 551 4, 2001. Synthetic work: (c) Piettre, A.; Chevenier, E.; Massardier, C.; Gimbert, Y.; Greene, A. E. *Org. Lett.* **2002**, *4*, 3139. (d) Chevenier, E.; Lucatelli, C.; Pandya, U.; Wang, W.; Gimbert, Y.; Greene, A. E. *Synlett* **2004**, 2693.
(6) Review: Dias, N.; Vezin, H.; Lansiaux, H.; Lansiaux, A.; Bailly, C. *Top. Curr. Chem.* **2005**, *253*, 89.
(7) (a) Kanai, Y.; Ishiyama, D.; Senda, H.; Iwatani, W.; Takahaski, H.; Konno, H.; Tokumasu, S.; Kanazawa, S. *J. Antibiot.* **2000**, *53*, 863. (b) Ishiyama, D.; Kanai, Y.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Kanazawa, S. *J. Antibiot.* **2000**, *53*, 873.
(8) Reported activity (ref 7): IC_{50} = 0.15 ng/mL for **3** vs 0.10 ng/mL for camptothecin.

10.1021/ol0617291 CCC: $33.50
Published on Web 09/15/2006

although synthetic studies toward these substances have been recorded in a dissertation.[9] In this paper, we describe a straightforward avenue to topopyrones that should be suitable for congener synthesis and structure−activity relationship (SAR) studies.

Exposure to alkali promotes facile rearrangement of angularly fused **1** and **2** to the corresponding linearly fused **3** and **4**.[7] This observation indicates that topopyrones B and D are thermodynamically favored relative to topopyrones A and C. Our avenue to **3** and **4** therefore relies on the cyclization of intermediate **5** under thermodynamically controlled conditions (Figure 2). Drawing upon the work of

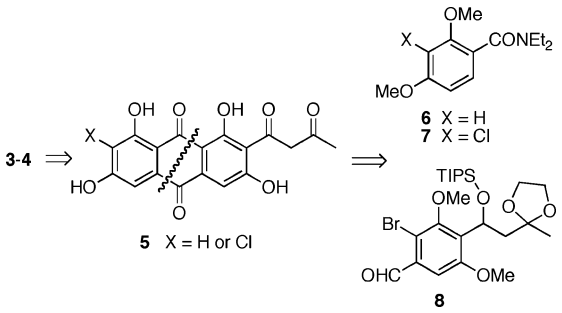
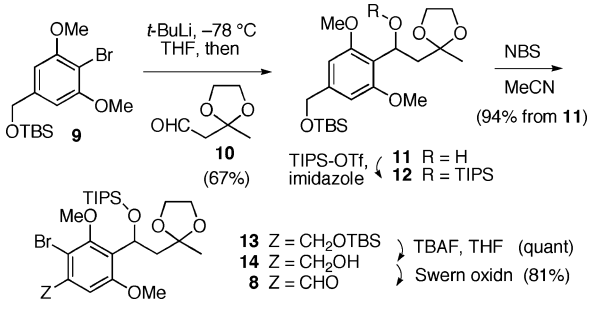


Figure 2. Retrosynthetic plan for topopyrones.

Snieckus,[10] we chose to assemble the anthraquinone core of the target molecules through the merger of fragments **6**−**8**, a transformation that may be achieved through a one-pot, three-step sequence.

The preparation of the "eastern" moiety **8**, which is common to all topopyrones, commenced with halogen−metal exchange of **9**[11] and addition of the resulting organometallic to aldehyde **10** (Scheme 1).[12] O-Silylation of the emerging

Scheme 1. Preparation of Fragment **8**



11 furnished **12**. Aromatic bromination followed by selective deprotection of the primary benzylic alcohol afforded **14**, which, upon Swern oxidation, yielded subtarget **8**.

It is noteworthy that the ^{1}H and ^{13}C NMR spectra of compounds **13**, **14**, and **8** indicated that these substances exist as mixtures of diastereomeric atropisomers. This was also the case for later intermediates incorporating fragment **8** and retaining the TIPS protecting group present therein. Atropisomerism disappeared upon release of the TIPS unit. A qualitative appreciation for these phenomena may be readily garnered through an inspection of molecular models of compounds **13**, **14**, and **8**: the bulky TIPS group greatly hampers rotation about the σ-bond connecting the benzylic carbon to the aryl segment.

No experiments were carried out to determine the coalescence temperature for atropisomer interconversion, let alone to measure conformational activation parameters. However, a rough estimate of the energy barrier for internal rotation in TIPS-protected intermediates was generated through a molecular mechanics study of model structure **15**. The optimized conformation of **15** is depicted in Figure 3

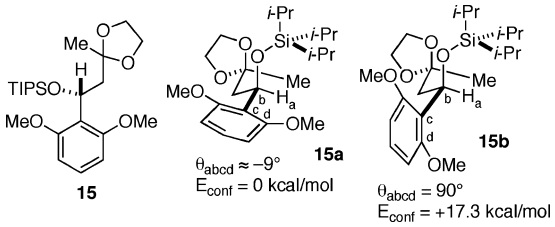


Figure 3. Computed conformational properties of model compound **15**.

as **15a**. The dihedral angle θ between the benzylic hydrogen and the *ortho*-aryl carbon atom is equal to approximately −9°. When θ was set to 90° and the remainder of the molecule was allowed to relax in the MM+ force field,[13] a conformer **15b** containing 17.3 kcal/mol of excess energy resulted. We regard this as the lower limit for the rotational barrier in such TIPS-protected molecules.[14]

The union of segment **8** with fragments **6** and **7** was achieved as outlined in Scheme 2. Thus, the Snieckus-type anion obtained upon directed metalation of benzamides **6** and **7** added to aldehyde **8** to form an intermediate presumed to be **16**. Treatment in situ with additional *tert*-BuLi presumably induced bromine−lithium exchange, thereby triggering cyclization of **16** to the corresponding dihydroanthraquinone. Exposure to air finally afforded the desired **17** and **18** in a yield of 17 and 20%, respectively, for the one-pot, three-step process (after purification).[15] In either case, debrominated compounds **19** and **20** were the major products (60−70% chromatographed).

(9) Qi, L. Dissertation; Brown University: Providence, RI, 2003: *Diss. Abstr. Int., B* **2003**, *64*, 1737.

(10) (a) Wang, X.; Snieckus, V. *Synlett* **1990**, 313. See also: (b) De Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802.

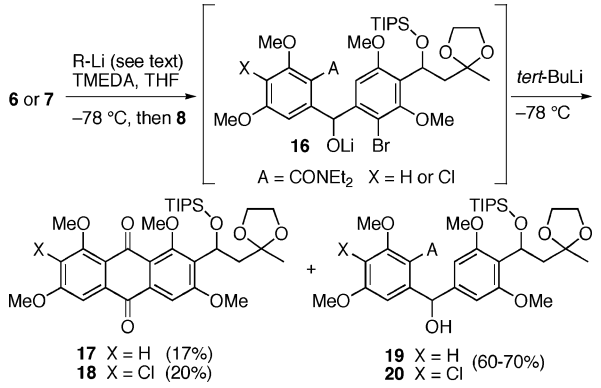
(11) The preparation of this material is described in the Supporting Information.

(12) Langer, P.; Freifeld, I. *Synlett* **2001**, *4*, 523.

(13) Calculations were performed with the Hyperchem package, available from Hypercube, Inc.

(14) The computed value is a lower limit for the rotational energy barrier (which is notoriously difficult to calculate with precision) because there is no actual eclipsing between the aryl carbons and the alkyl or OTIPS residues.

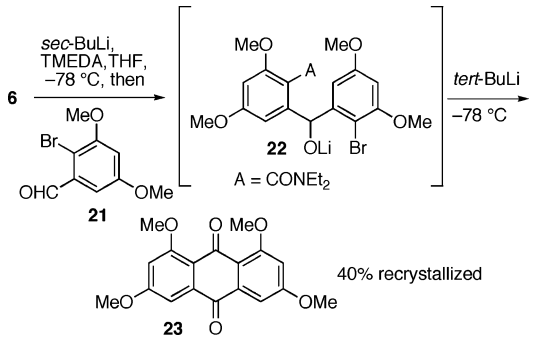
Scheme 2. Anthraquinone Assembly



Several comments are in order at this juncture. First, deprotonation of **6** occurred rapidly with the standard *sec*-BuLi/TMEDA combination (1.05 equiv, 3 h, −78 °C).[16] By contrast, chlorinated benzamide **7**[11] proved to be remarkably resistant to deprotonation under the same conditions, even when exposed to the action of a 5-fold molar excess of the *sec*-BuLi/TMEDA complex (no incorporation of deuterium upon quenching with CD_3OD). Ultimately, deprotonation was effected by the use of the more basic *tert*-BuLi/TMEDA system (1 equiv, 3 h, −78 °C; essentially complete deuteration upon a CD_3OD quench). The reason(s) for such difficulties remain unclear. A number of chlorinated benzamides undergo deprotonation in a normal fashion,[12] signaling that the behavior of **7** cannot be attributed to the chloro substituent per se. It is likewise difficult to impute the foregoing problems to sequestration of the base through coordination/chelation[17] effects involving the chlorine atom because amide **7** resisted deprotonation even in the presence of excess base and because, e.g., 2,3,4-trimethoxybenzamide (an analogue of **7** wherein a methoxy group replaces the chloro substituent) undergoes directed ortho metalation without incident,[18] even though the triad of adjacent methoxy groups undoubtedly can coordinate/chelate/sequester organolithium species at least as effectively as the 2,4-dimethoxy-3-chloro arrangement present in **7**.

Second, the genesis of products **19** and **20** is not attributable to an insufficient time allotted to the cyclization step. To wit, the yield and the ratio of desired **17** and **18** to undesired **19** and **20** remained essentially unchanged when, following addition of *tert*-BuLi to the solution containing **16**, the mixture was allowed to stir for a period ranging from 3 to 12 h. Moreover, the construction of 1,3,6,8-tetramethoxy-anthraquinone **23** by the same method was significantly more efficient, providing recrystallized product in 40% yield (Scheme 3, the crude yield of **23** was at least

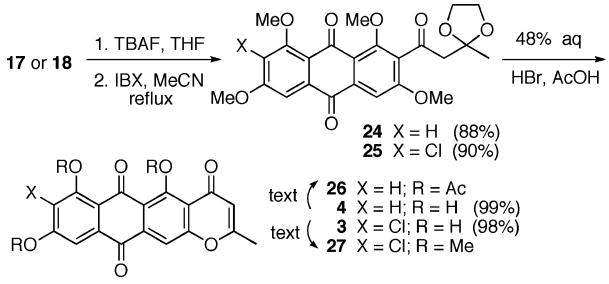
Scheme 3. Synthesis of Anthraquinone **20**



60%). We therefore suspect that parasitic proton-transfer events, perhaps from one of the benzylic positions of the presumed aryllithium derivative of **16**, consume transient organometallic species, resulting in the formation of **19** and **20** while eroding the overall yield of the targets **17** and **18**.

Conversion of **17** and **18** to topopyrones D and B entailed desilylation and IBX oxidation of the resulting alcohol,[19] followed by exposure of ketones **24** and **25** to 48% aqueous HBr solution (Scheme 4). Topopyrone D was characterized

Scheme 4. Synthesis of Topopyrones B and D



as such.[20] However, the isolation paper[7] provides no spectral properties for free **3** and **4**, which were instead characterized as the respective triacetate and trimethyl derivatives. This is probably a consequence of the poor solubility of topopyrones in common organic solvents. Accordingly, fully synthetic **3** and **4** were converted to trimethyl ether **27** and triacetate **26**, respectively. These derivatives produced spectra that were in complete accord with the data reported for their naturally derived counterparts.[7]

In summary, we have devised a straightforward avenue to topopyrones that should be suitable for congener synthesis and SAR studies. This would entail the use of suitably

(15) These yields are somewhat disappointing. However, the one-pot process of Scheme 2 permits a high degree of convergency, and it involves three distinct, sequential reactions (nucleophilic addition of the lithiated benzamide to **8**, halogen−metal exchange, and intramolecular addition of the aryllithium derivative of **16** to the amide carbonyl). An overall yield of 20% thus corresponds to an average 58% yield per step.

(16) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(17) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(18) Sibi, M. P.; Jalil Miah, M. A.; Snieckus, V. *J. Org. Chem.* **1984**, *49*, 737.

(19) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(20) See Supporting Information for pertinent data.

modified fragments **6**−**8** in the sequence outlined in Scheme 2. Improved variants of the approach described herein are under development, and additional results in this area will be described in due course.

Acknowledgment. We thank Prof. V. Snieckus, of Queen's University, Kingston, ON, for helpful discussion and the University of British Columbia, NSERC, the Canada Research Chair Program, and MerckFrosst Canada for financial support.

Supporting Information Available: Experimental procedures, characterization data, and spectra of all the compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0617291