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SYNTHESES AND BIOLOGICAL EVALUATION OF TWO NEW NAPROXEN ANALOGS

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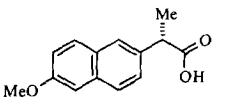
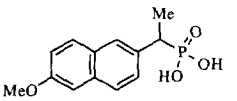
Abstract: Reported herein are the syntheses and biological activities of two structural analogues (**2** and **3**) of naproxen (**1**).Copyright © 1996 Elsevier Science Ltd

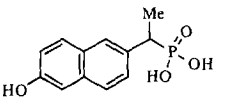
For over thirty years, research efforts have been directed towards the discovery of new nonsteroidal antiinflammatory agents.[1] Currently, (+)-6-methoxy-α-methyl-2-naphthaleneacetic acid (naproxen, **1**) is one of the most widely prescribed drugs in this class, showing both antiinflammatory and analgesic activities.[2] While a plethora of structural analogs of naproxen exist,[2] interestingly there have been no reports on phosphonic acid analogs of this compound. As such we designed two expedient routes and employed them in the synthesis of naproxen phosphonic acid analogs **2** and **3**. We report the activity of these analogs in two cyclooxygenase assays.



1



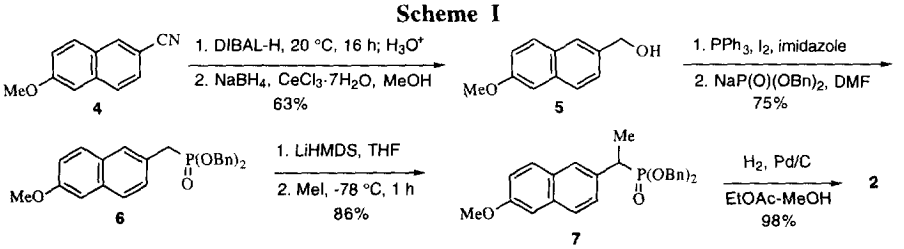
2



3

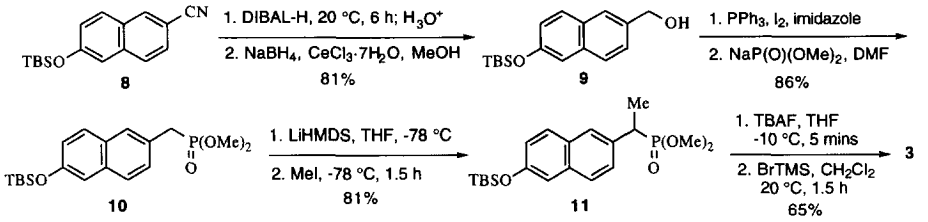
The naproxen analog **2** was prepared from **4** as shown in Scheme I. Upon sequential reduction of nitrile **4**, the resulting alcohol **5** was converted to the corresponding iodide that was treated with a mixture of sodium hydride and dibenzyl phosphite to provide phosphonate **6** in 75% yield. Methylation of the phosphonate **6** using lithium hexamethyldisilazide and iodomethane proceeded in 86% yield to give **7**, with no accompanying double alkylation product. Hydrogenolysis of **7** secured the naproxen analog **2**.

Scheme I



4 **5** **6** **7**

Scheme II



As illustrated in Scheme II, naproxen analog **3** was synthesized from the nitrile **8**, which was obtained from commercially available **4**.[3] Utilizing a similar synthetic scheme (vide supra), dimethyl phosphonate **11** was prepared from **8**. Again, only mono-alkylation was observed and the resulting phosphonate **11** was subjected to desilylation followed by demethylation, furnishing the naproxen analog **3**.

The biological activities of these analogs were examined in two cyclooxygenase assays. The compounds were tested at 10 μM, in vitro against human platelet Cox-1[4] and human umbilical cord endothelial cells (ECV-304 cell line) Cox-2.[5] Naproxen typically inhibits Cox-1 with an IC_{50} of 0.35 ± 0.08 μM, and Cox-2 with an IC_{50} of 24.3 ± 3.9 μM. Our analog **2** showed 32% inhibition for both cell lines, while **3** displayed 19% and 31% inhibition against Cox-1 and Cox-2, respectively. Neither analog was as potent as **1**, however, even in racemic form both displayed activity and **3** showed modest selectivity between the Cox-1 and Cox-2 assays. These results coupled with the simplicity of our synthetic operations, potential points of attachment for added diversity make these approaches attractive for combinatorial efforts. Future plans will address these possibilities.

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REFERENCES AND NOTES

1. (a) Shen, T. Y. *Annu. Rep. Med. Chem.* **1967**, 215. (b) Shen, T. Y. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 460. (c) Sanders, H. J. *C&EN* **1968**, *46 (34)*, 46.
2. For naproxen and representative analogs, see: (a) Pala, G.; Bruzzese, T.; Marazzi-Uberti, E.; Coppi, G. *J. Med. Chem.* **1966**, *9*, 603. (b) Harrison, I. T.; Lewis, B.; Nelson, P.; Rooks, W.; Roszkowski, A.; Tomolonis, A.; Fried, J. H. *J. Med. Chem.* **1970**, *13*, 203. For biological evaluation, see: (c) Roszkowski, A. P.; Rooks II, W. H.; Tomolonis, A. J.; Miller, L. M. *J. Pharm. Exp. Ther.* **1971**, *179*, 114. (d) Tomlinson, R. V.; Ringold, H. J.; Qureshi, M. C.; Forchielli, E. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 552. (e) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1979**, *18*, 241.
3. Cleavage of the methyl ether of **4** was accomplished by employing BBr_3; the resulting alcohol was protected as its silyl ether using a combination of TBSCl and imidazole.
4. The production of thromboxane B_2 was measured by radioimmunoassay (RIA).
5. Prostaglandin E2 levels were measured by RIA following the addition of arachidonic acid to cells.

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