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Synthesis of 'Spacer'-Naproxen [2-(6-Methoxybiphenylen-2-yl)propanoic Acid] and -Isonaproxen [2-(7-Methoxybiphenylen-2-yl)propanoic Acid]

Juan A. González Gómez

James R. Green
University of Windsor

Peter C. Vollhardt
University of California - Berkeley

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Juan A. González Gómez, James R. Green, K. Peter C. Vollhardt*

Department of Chemistry, University of California at Berkeley, Berkeley, CA 94720-1460, USA
Fax +1(510)6435208; E-mail: kpcv@berkeley.edu

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Abstract: The $CpCo(CO)_2$-catalyzed cocyclization of 1,2-diethynyl-4-methoxybenzene with alkynes can be applied to the synthesis of 'spacer'-naproxen [2-(6-methoxybiphenylen-2-yl)propanoic acid] and its 7-methoxy isomer, 'spacer'-isonaproxen. While unsymmetrical alkynes are incorporated without regioselectivity, the methoxy group in 6-methoxy-2,3-bis(trimethylsilyl)biphenylene directs electrophiles to C-3, thus allowing for regiochemical differentiation between the 2- and 3-positions.

Key words: alkynes, cobalt, cyclization, carbocycles, regioselectivity

Dimensional probes in the form of structural spacers separating functional units have been used in various areas of structure–activity correlations. The smallest spacer between two rings is two bonds, in the case of aromatic cycles engendering a cyclobutadiene core. From this perspective, biphenylene is 'spacer'-naphthalene. This motif has been exploited to investigate electron-transfer mechanisms between electroactive units,[1] bidentate Lewis and Brønsted acid effects,[2] potential utility in supramolecular assembly,[3] steric interference,[4] spatial boundaries for biomolecular interactions,[5] and novel drug topologies.[6] In tune with continuing interest in the development of new cyclooxygenase (Cox) inhibitors,[7] we report the synthesis of the spacer analogues of the anti-inflammatory drug naproxen (**1**)[8] and its regioisomer isonaproxen, namely compounds **2** and **3** (Figure 1), and the preliminary biological evaluation of the former.

The strategy for their construction was based on our cobalt-catalyzed assembly of biphenylenes by alkyne cyclotrimerization[9] and the hitherto unexplored potential of remote substituents on its regiochemical control.[10]

The work began with a test of the basic feasibility of the approach featuring 2-(biphenylen-2-yl)acetic acid **4** as the target. The two reported syntheses of this molecule[6k,11] suffer from the need for biphenylene as the starting material.[12] A more convergent execution is depicted in Scheme 1, which entails the $CpCo(CO)_2$-catalyzed cocyclization of diyne **5**[9b] with an excess of the homopropargyl alcohol/ether substrates **6** (**6a**, neat; **6b**, 4 equiv in THF; **6c**, 5 equiv in THF). Fully silylated **6c** fared best, affording **7c** in 52% yield. Compound **7c** was in turn deprotected with fluoride and oxidized with pyridinium dichromate[13] to render **4** (overall, unoptimized yield from **5**: 13%).[14]

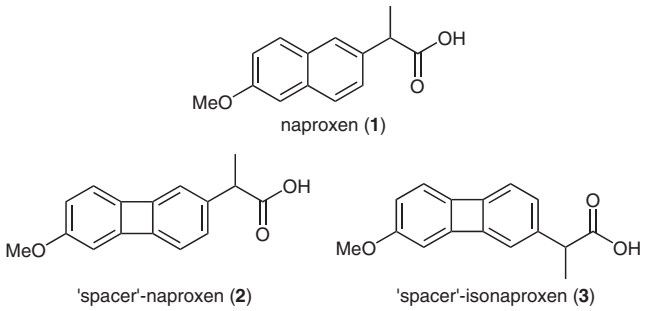
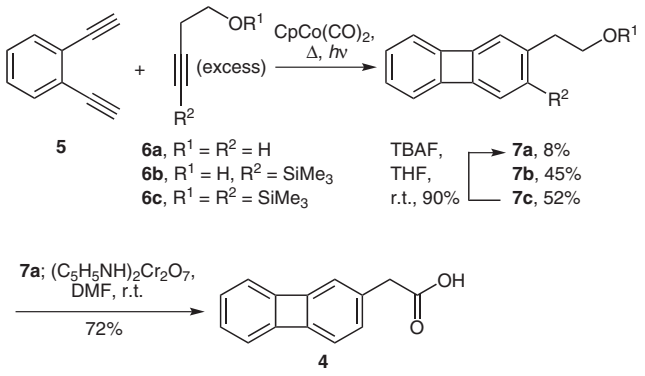


Figure 1



Scheme 1

Next was the task of establishing the efficacy, in addition to regioselectivity, of cycloadditions to the methoxy-bearing diyne **8**[15] to alkynes **9** (Scheme 2). The corresponding biphenylenes **10** ensued in reasonable to good yields.[14] Disappointingly, however, the unsymmetrical substrates **9b** and **9c** led to the two regioisomers **A** and **B** of **10b** and **10c**, respectively, as an unseparated equimolar mixture. What is the origin of this outcome? Mechanistically, it is likely that initial cobaltacyclopentadiene formation involves intermolecular coupling of **9** with either one of the diyne units of **8** to give **C** or **D** (Scheme 2), in this way deferring formation of the strained ring until the final step of the cyclotrimerization.[16,17] Moreover, it is expected that the bulky TMS group will emerge positioned α to Co in this transformation. Therefore, the indiscriminate emergence of **A** and **B** in Scheme 2 signals that the triple bonds in **8** exhibit equal propensity for oxidative coupling, gen-

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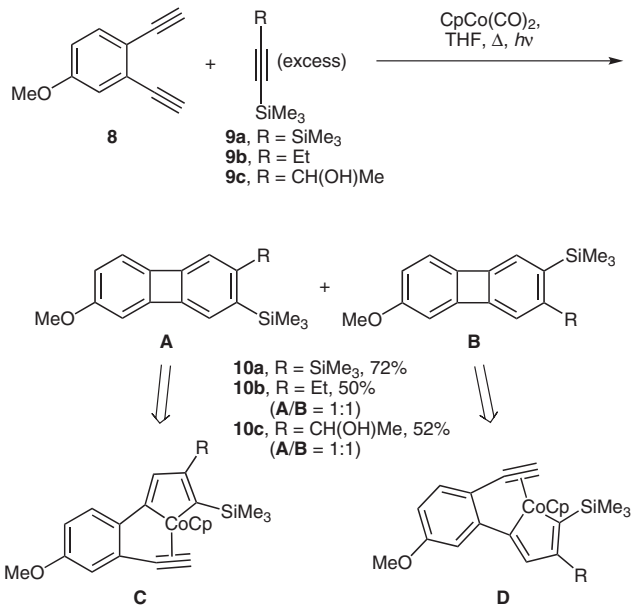
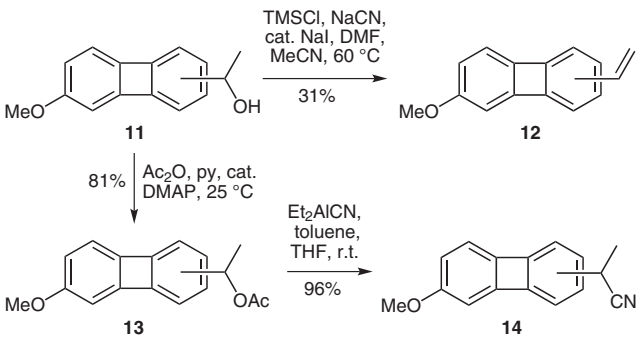
erating equal amounts of **C** and **D**, thus establishing the absence of any remote electronic effect of the MeO group on this step.



Scheme 2

The lack of regioselectivity in the formation of **10b** and **10c** notwithstanding, we forged ahead with **10c** in an attempt to complete the syntheses of the target compounds, relying on established sequences toward anti-inflammatory 2-arylpropanoic acids.[8,18] For this purpose, **10c** was first desilylated with TBAF (THF, 92%) to render **11**. Attempted direct cyanation[19] generated only ethenylbiphenylene derivatives **12** (Scheme 3), but an indirect route,[20] via acetates **13**, succeeded in attaining **14**.[14] While preliminary small-scale experiments indicated the formation of mixtures of **2** and **3** on nitrile hydrolysis, this approach was abandoned, because of the failure to separate the regioisomers at any step along the sequence and because a solution to the regioselectivity problem was found, as described next.

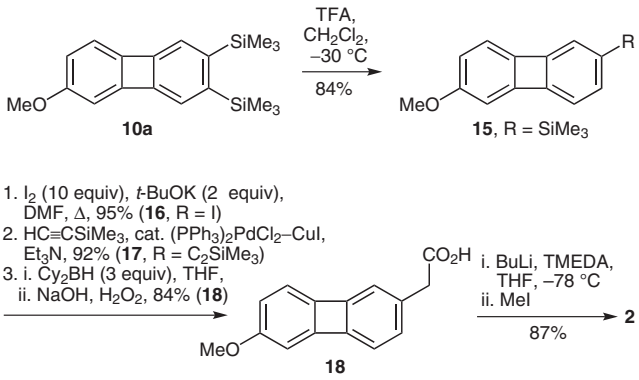
The key to the selective synthesis of **2** and **3** was the directing influence of the 6-methoxy substituent on the regioselectivity of attack by electrophiles at C-3 in the



Scheme 3

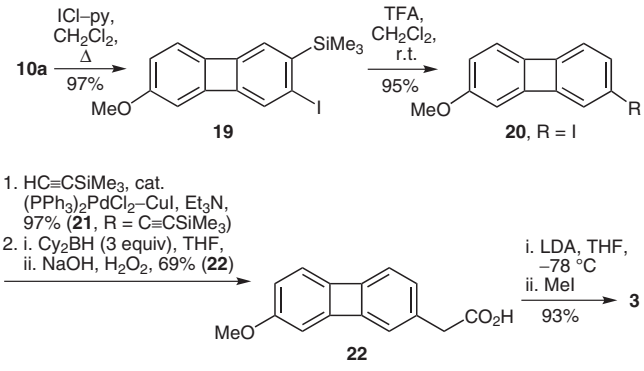
bis(trimethylsilyl)derivative **10a**.[21] Thus, quantitative low-temperature protodesilylation with TFA produced **15** (Scheme 4) admixed with small amounts of its regioisomer (86:14), from which **15** was removed by fractional crystallization.[14] The position of the silyl group was ascertained by 2D NMR correlation spectroscopy, necessitating the complete assignment of both ^{1}H and ^{13}C spectra.[14] Chemical confirmation was attained by hydrogenolysis of the four-membered ring bonds (Ra-Ni, EtOH, heat, 57%)[21] leading to 4-methoxy-3′-(trimethylsilyl)- and 3-methoxy-4′-(trimethylsilyl)biphenyl, separated by GC and identified by the respective presence of only one *para*- and one *meta*-substituted phenyl group in each (^{1}H NMR). The regioisomer of **15** would have led to bis-*para*- and bis-*meta*-substituted biphenyls, clearly incompatible with the observed data.[14]

With **15** in hand, the synthesis of 'spacer'-naproxen **2** was completed as depicted in Scheme 4. Thus, base-mediated[22] iododesilylation furnished **16**, which was alkynylated to **17** and then converted to acid **18** following Zweifel's procedure.[23] Finally, methylation provided the desired target in good overall yield.[14]



Scheme 4

The directing power of the methoxy substituent is also effective in the synthesis of the regioisomeric series corresponding to that in Scheme 4 by simply inverting the sequence of the first two steps starting from **10a** (Scheme 5).



Scheme 5

Hence, iododesilylation with ICl–pyridine complex[24] furnished **19** exclusively, which, on treatment with acid, delivered **20**. From there, 'spacer'-isonaproxen **3** was readily assembled through the intermediacy of **21** and **22**.[14]

'Spacer'-naproxen **2** was tested in vitro for its effects on lipoxygenase and cyclooxygenase. It was inactive against the former, but as active as naproxen against the latter. However, in vivo oral testing failed to show any cyclooxygenase inhibitory function, possibly a result of poor absorption or rapid metabolism.

To summarize, we have found that a 4-methoxy group in *ortho*-diethynylbenzene has no influence on the regioselectivity of the cobalt-catalyzed [2+2+2] cycloaddition with unsymmetrical alkynes. In contrast, this group at C-6 of the biphenylene nucleus allows the selective stepwise replacement of the silyl groups of the 2,3-bis(trimethylsilylated) second arene ring by electrophiles. This feature significantly expands the accessibility of specifically substituted biphenylenes, as demonstrated by the syntheses of the biphenylene analogues of naproxen and isonaproxen.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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