Diastereoselective [4+2] Reactions of *o*-Quinone Methides with a Chiral Enol Ether: Asymmetric Synthesis of (+)-*R*-Mimosifoliol

Carolyn Selenski, Lupe H. Mejorado, Thomas R. R. Pettus*

Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, CA 93106-9510, USA
Fax +1(805)8935690; E-mail: pettus@chem.ucsb.edu

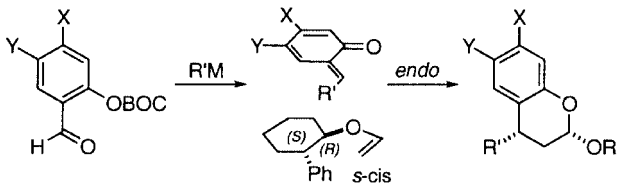
Received 20 February 2004

Abstract: The first examples of enantioselective [4+2] cycloadditions of *o*-quinone methides (*o*-QMs) are reported. Their cycloaddition with *trans*-2-phenyl-1-cyclohexanol derived vinyl ether produces chiral benzopyrans. This procedure offers access to chiral aliphatic benzylic carbons and is applied to the synthesis of (+)-*R*-mimosifoliol.

Key words: benzylic stereocenter, *o*-quinone methide, Diels–Alder, asymmetric [4+2] cycloaddition, inverse demand, chiral enol ethers, lactol, chroman, benzopyran, total synthesis

Recently, our group had shown *o*-QMs undergo extremely *endo* selective inverse demand [4+2] cycloadditions with vinyl ethers, furans, enamines and imines in good yields triggered by an assortment of organometallic reagents.[1] In the past, chiral enol ethers have exerted facial selectivity in a variety of [4+2] reactions.[2] Therefore, we envisioned such a process with *o*-QMs to be beneficial for enantioselective chroman synthesis and practical for the construction of benzylic alkyl stereocenters. To date the preferred methods have been catalytic asymmetric hydrogenation and asymmetric conjugate addition. However, these processes often require lengthy reaction times and their success are often substrate dependent.[3]

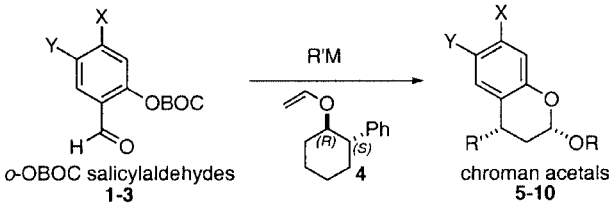
We recently completed a concise synthesis of (±)-**15**,[4] which was isolated from the rootwood of *Aeschynomene mimosifolia* Vatke (Leguminosae).[5] Despite many attempts, we were unable to develop an asymmetric variant of the sequential *o*-QM formation and consumption process previously used. A catalytic method for asymmetric induction would be preferred;[6] however, it appears that *o*-QMs are so reactive that catalysts would only facilitate dimerization. Therefore, we chose to investigate [4+2] cycloadditions of *o*-QMs and chiral enol ethers (Scheme 1). Such an asymmetric process should provide rapid access to an assortment of chiral benzopyrans.



Scheme 1 Enantioselective synthesis of chromans

SYNLETT 2004, No. 6, pp 1101–1103
Advanced online publication: 25.03.2004
DOI: 10.1055/s-2004-822888; Art ID: S00404ST

Table 1 Diastereoselectivities of **4** with Various *o*-QM Nuclei



RMgBr (1.05 equiv) added to solution of the *o*-OBOC benzaldehyde (0.1 M Et_2O) and enol ether **4** (2 equiv) at –78 °C and warmed to r.t. over 3 h.

Entry	Aldehyde	RM	Selectivity *endo*:*endo*:*exo*:*exo*	Yield
1	**1**: X = -OBOC, Y = -OMe	PhMgBr	>50:1:0:0	62% of **5**
2	**1**: X = -OBOC, Y = -OMe	MeMgBr	>50:1:0:0	75% of **6**
3	**2**: X = -OBOC, Y = -H	PhMgBr	>50:1:0:0	88% of **7**
4	**2**: X = -OBOC, Y = -H	MeMgBr	>50:1:0:0	72% of **8**
5	**3**: X = -O(CH$_2$)$_2$TMS, Y = -OMe	PhMgBr	>50:1:0:0	83% of **9**
6	**3**: X = -O(CH$_2$)$_2$TMS, Y = -OMe	MeMgBr	>50:1:0:0	74% of **10**

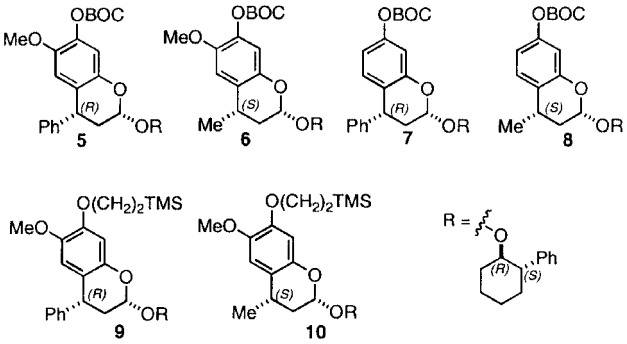


Figure 1

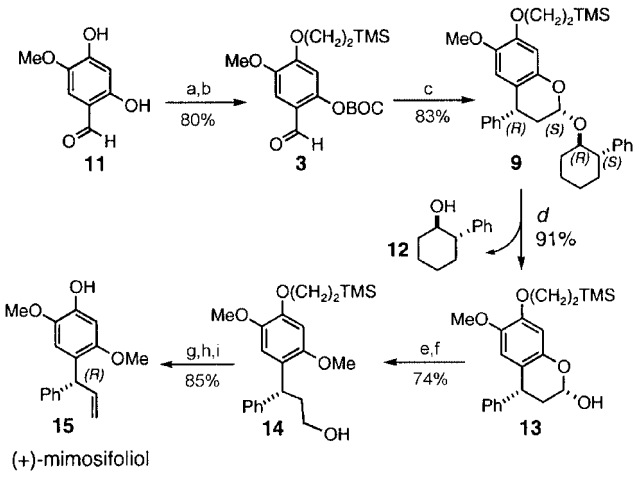
The difficulty associated with the past syntheses of chiral enol ethers has made their subsequent application in synthesis somewhat unattractive.[7] Recently, however, the Ishii method enables the preparation of enol ethers in yields >95% from the corresponding chiral alcohol, vinyl

acetate, Na_2CO_3, and $Ir_2Cl_2[cod]_2$ catalyst.[8] This process has greatly improved the accessibility of chiral vinyl ethers.

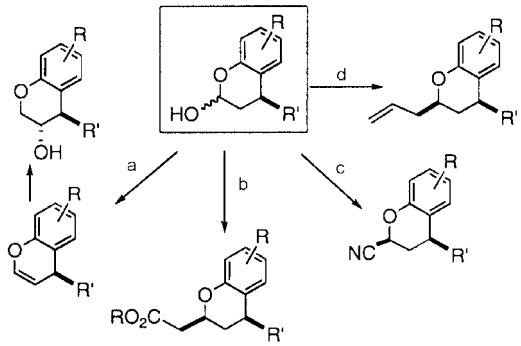
Many chiral enol ethers were considered. The *trans*-2-phenyl-1-cyclohexanol derived vinyl ether[9] was the most diastereoselective displaying >98% de in all cases examined and affording the benzopyrans **5**–**10**[10] in respectable yields ranging from 62–88% (Table 1, entries 1–6, Figure 1). Moreover, the corresponding chiral alcohol **12** is commercially available in both enantiomeric forms. An asymmetric synthesis of (+)-**15** was carried out to ascertain the direction of asymmetric induction (*R* or *S*) afforded by the 2*S*-phenyl-1*R*-cyclohexanol derived vinyl ether (–)-**4** and illuminate the orientation of reactants in the transition state.

The synthesis began by treatment of benzaldehyde **11**[11] under a Mitsunobu protocol [1 M THF, 2 equiv $TMS(CH_2)_2OH$, PPh_3, and DIAD] followed by carbonate formation (1 M CH_2Cl_2, 1.1 equiv BOC_2O, 0.5 equiv Hunig's base, cat. DMAP) resulting in the bis-protected aldehyde **3**[12] in 80% yield. When **3** (0.1 M Et_2O) was subjected to PhMgBr (1.05 equiv) in the presence of enol ether (–)-**4** (2.0 equiv) at –78 °C and warmed over 3 hours, adduct (+)-**9**[13] arose in 83% yield. A 500 MHz 2D NOESY experiment established the stereochemical relationship between the benzopyran substituents and those of the chiral auxiliary. Hydrolysis of **9** (0.1 M, 1:1 H_2O–CH_3CN, 0.6 equiv CSA, 70 °C, 6 h) afforded the lactol **13**[14] in 91% along with the chiral alcohol (–)-**12**, which could be reused for subsequent construction. Reduction of the lactol **13** (0.1 M THF, 3 equiv LAH, 0 °C, 5min) followed by methylation (1 M Et_2O, 3 equiv CH_2N_2, 12 h) afforded the primary alcohol (+)-**14**[15] in a 74% yield. Introduction of the desired alkene was accomplished by the conversion of the primary alcohol **14** into the corresponding selenide (0.1 M THF, 2 equiv PhSeCN, 2 equiv PBu_3, r.t., 5 h) followed by oxidation (0.5 M, 2:1 MeOH–H_2O, 2 equiv $NaIO_4$, 2 equiv $NaHCO_3$, 40 °C) which resulted in spontaneous *syn*-elimination. Finally, cleavage (0.2 M DMF, 2 equiv CsF, 160 °C, 6 h) of the O-$(CH_2)_2$TMS ether afforded synthetic *R*-mimosifoliol (+)-**15** $[\alpha]_D^{25}$ = + 20 °C (*c* = 1.0, $CHCl_3$), which was identical in every respect to (+)-**15** isolated from natural sources. Because the desired (*R*)-enantiomer of **15** was obtained from the (–)-*trans*-2*S*-phenyl-cyclohexan-1*R*-ol derived vinyl ether, it appears that chiral enol ether (–)-**4** undergoes cycloaddition with the *o*-QM through an *endo* transition state via its *s-cis* conformation on the π-face opposite the phenyl ring.

Lactols similar to **13** undergo many chemical transformations including elimination (MsCl, TEA) affording the corresponding chromene that can be regioselectively functionalized (Scheme 3, reaction a).[16] In addition, related lactols undergo homologation with ylides to afford an extended benzopyran ester (Scheme 3, reaction b),[17] as well as addition of trimethylsilylcyanide and allyl silane under Lewis acid mediation, (Scheme 3, reactions c and d).[18] With numerous lactol transformations, we expect that our asymmetric procedure could prove useful in other synthetic endeavors; such as, the syntheses of molecules resembling (+)-*R*-tolterodine[19] and (–)-heliannuol E.[20]



Scheme 2 Synthesis of (+)-mimosifoliol (**15**).
Reaction Conditions: a) $TMS(CH_2)_2OH$ (2 equiv), PPh_3 (2 equiv), DIAD (2 equiv), 1 M THF, 12 h. b) BOC_2O (1.1 equiv), Hunig's base (0.5 equiv), DMAP (cat.), 0.1 M CH_2Cl_2. c) PhMgBr, (1.05 equiv), **4** (2 equiv) in 0.1 M Et_2O, –78 °C to r.t., 3 h. d) CSA (0.6 equiv), 0.1 M 1:1 H_2O–CH_3CN, 70 °C, 5 h. e) $LiAlH_4$ (2 equiv), 0 °C, 5 min. f) CH_2N_2. g) PhSeCN (1.05 equiv), PBu_3 (1.1 equiv). h) $NaIO_4$, $NaHCO_3$, 40 °C. i) CsF (2 equiv), 0.1 M DMF, 160°C, 6 h.



Scheme 3 a) MsCl, Et_3N. b) $Ph_3P{=}CHCO_2R$. c) ZnI_2, TMSCN. d) $BF_3{\cdot}Et_2O$, $CH_2{=}CHCH_2TMS$.

Acknowledgment

Research Grants from the UC Committee on Cancer Research (19990641) and (SB010064), and the National Science Foundation (Career-0135031) are greatly appreciated.

References

(1) (a) Van De Water, R.; Magdziak, D.; Chau, J.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502. (b) Jones, R. M.; Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2002**, *67*, 6911.
(2) (a) Posner, G.; Wettlaufer, D. G. *Tetrahedron Lett.* **1986**, *27*, 667. (b) Choudhury, A.; Franck, R. W.; Gupta, R. B. *Tetrahedron Lett.* **1989**, *30*, 4921. (c) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (d) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1996**, *37*, 4007. (e) Prapansiri, V.; Thornton, E. R. *Tetrahedron Lett.* **1991**, *32*, 3147.

(3) (a) Bissel, P.; Nazih, A.; Sablong, R.; Lepoittevin, J.-P. *Org. Lett.* **1999**, *1*, 1283. (b) Johnson, S. J.; Evans, D. A. *Acc. Chem. Res.* **1999**, *33*, 325.
(4) Tuttle, K.; Rodriguez, A. A.; Pettus, T. R. R. *Synlett* **2003**, 2234.
(5) Fullas, F.; Kornberg, L. J.; Wani, M. C.; Wall, M. E. *J. Nat. Prod.* **1996**, *59*, 190.
(6) (a) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563. (b) Juhl, K.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498.
(7) (a) Watanabe, W. H.; Conlon, L. W. *J. Org. Chem.* **1957**, *79*, 2828. (b) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653.
(8) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590.
(9) (a) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205. (b) Denmark, S. E.; Marcin, L. R.; Schnute, M. E.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205.
(10) **Compound 5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.07 (m, 10 H), 6.67 (s, 1 H), 6.20 (s, 1 H), 4.46–4.43 (m, 1 H), 3.75–3.71 (m, 1 H), 3.66–3.65 (m, 1 H), 3.53 (s, 3 H), 2.47–2.46 (m, 1 H), 2.31–2.30 (m, 1 H), 1.90 (m, 6 H), 1.55 (s, 9 H), 1.51–1.27 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 147.4, 145.4, 144.3, 144.2, 139.6, 128.8, 128.6, 128.3, 128.3, 126.8, 126.5, 123.3, 113.4, 111.7, 101.0, 84.4, 83.6, 56.6, 51.6, 41.4, 37.1, 34.9, 32.7, 27.8, 25.9, 25.5. **Compound 6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.19 (m, 5 H), 6.66 (s, 1 H), 6.59 (s, 1 H), 4.41–4.39 (m, 1 H), 3.77 (s, 3 H), 3.65–3.63 (m, 1 H), 2.61–2.49 (m, 2 H), 2.22–2.20 (m, 1 H), 1.91–1.56 (m, 6 H), 1.55 (s, 9 H), 1.54–1.22 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8, 146.2, 145.5, 144.5, 139.2, 128.3, 128.2, 126,4, 126.6, 111.8, 111.6, 100.4, 83.8, 83.5, 56.8, 51.7, 35.4, 34.9, 33.0, 28.1, 27.8, 26.0, 25.5, 21.7. **Compound 7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.05 (m, 10 H), 6.68–6.51 (m, 2 H), 4.51–4.48 (m, 1 H), 3.72–3.66 (m, 2 H), 2.53–2.33 (m, 2 H), 1.91–1.62 (m, 3 H), 1.55 (s, 9 H), 1.49–1.28 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 152.1, 150.5, 144.2, 130.0, 128.8, 128.7, 128.3, 128.3, 126.9, 123.5, 113.7, 110.2, 101.4, 84.5, 83.6, 51.6, 41.1, 36.8, 35.0, 32.7, 27.9, 26.0, 25.5. **Compound 8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.00 (m, 5 H), 6.89–6.59 (m, 2 H), 4.46–4.44 (m, 1 H), 3.70–3.64 (m, 1 H), 2.62–2.50 (m, 2 H), 2.23–2.21 (m, 1 H), 1.92–1.58 (m, 3 H), 1.55 (s, 9 H), 1.46–1.21 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 152.2, 150.2, 144.5, 128.3, 128.2, 128.0, 126.5, 125.4, 113.6, 110.2, 100.7, 83.9, 51.7, 35.5, 34.9, 33.0, 29.9, 27.9, 27.8, 26.0, 25.5, 21.4. **Compound 9**: See ref. 13.
(11) Demyttenaere, J.; Van Syngel, K.; Peter Markusse, A.; Vervisch, S.; Debenedetti, S.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2163.
(12) **Compound 3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (s, 1 H), 7.32 (s, 1 H), 6.69 (s, 1 H), 4.19 (t, *J* = 8.4 Hz, 2 H), 3.91 (s, 3 H), 1.59 (s, 9 H), 1.25 (t, *J* = 8.4 Hz, 2 H), 0.10 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2, 154.5, 151.9, 148.3, 147.7, 120.6, 109.7, 106.6, 84.7, 67.3, 56.4, 27.9, 17.7, -1.3. IR (CH_2Cl_2): 2956, 2933, 2857, 1761, 1681, 1607, 1512.1, 1275 cm^{-1}. LRMS (EI): *m*/*z* calcd for $C_{18}H_{28}O_6Si$: 368; found: 368.
(13) **Compound 9**: $[\alpha]_D^{25}$ = +15 °C (*c* = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.21 (m, 10 H), 6.37 (s, 1 H), 6.11 (s, 1 H), 4.47–4.45 (m, 1 H), 4.09–4.05 (t, *J* = 8.3 Hz, 2 H), 3.74–3.56 (m, 2 H), 3.54 (s, 3 H), 2.51–2.45 (m, 1 H), 2.35–2.23 (m, 1 H), 1.91–1.19 (m, 11 H), 0.09 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 147.5, 144.9, 144.2, 143.7, 128.7, 128.4, 128.2, 127.4, 126.6, 126.4, 115.8, 112.7, 102.2, 101.1, 84.3, 66.3, 56.5, 51.6, 41.0, 37.4, 35.0, 32.7, 25.9, 25.4, 17.9, –1.3. IR (CH_2Cl_2): 2934, 2858, 1618, 1600, 1504, 1494, 1407, 1252 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{33}H_{42}O_4Si$: 530.7697; found: 530.2835.
(14) **Compound 13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5 H), 6.43 (s, 1 H), 6.26 (s, 1 H), 5.60–5.58 (m, 1 H), 4.27–4.23 (m, 1 H), 4.08 (t, *J* = 8.5 Hz, 2 H), 3.59 (s, 3 H), 2.29–2.23 (m, 1 H), 2.17–2.06 (m, 1 H), 1.23–1.21 (t, *J* = 8.5 Hz, 2 H), 0.07 (s, 2 H).
(15) **Compound 14**: $[\alpha]_D^{25}$ = +41 °C (*c* = 0.37, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.16 (m, 5 H), 6.68 (s, 1 H), 6.47 (s, 1 H), 4.53–4.49 (m, 1 H), 4.14–4.13 (m, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.90–2.87 (m, 2 H), 2.45–2.39 (m, 2 H), 1.24–1.21 (m, 2 H), 0.12 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 147.5, 144.9, 128.5, 128.2, 126.2, 124.7, 113.2, 100.0, 76.7, 66.9, 61.3, 57.1, 57.0, 38.8, 37.9, 18.1, –1.2. IR (CH_2Cl_2): 3688, 3053, 2955, 2933, 1607, 1506, 1274 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{22}H_{32}O_4Si$: 388.5726; found: 388.2083.
(16) Miki, Y.; Hachiken, H.; Nogurchi, K.; Ohta, M.; Nakano, A.; Takahashi, N.; Takemura, S. *Chem. Pharm. Bull.* **1990**, *38*, 3257.
(17) Cohen, N.; Weber, G. F. Hoffmann-La Roche F. & Co. A.-G. Switzerland Eur. Pat. Appl. EP 84107289, 19840625, **1985**, 109.
(18) (a) Ku, Y.-Y.; Grieme, T.; Raje, P.; Sharma, P.; Morton, H. E.; Rozema, M.; King, S. A. *J. Org. Chem.* **2003**, *68*, 3238. (b) Fontana, E.; Vicario, G. P.; Melloni, P. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 1035.
(19) Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Org. Process Res. Dev.* **2002**, *6*, 379.
(20) Macas, F. A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Tetrahedron Lett.* **1999**, *40*, 4725.