New Strategy for the Stereocontrolled Construction of Decalins and Fused Polycycles *via* a Tandem Diels−Alder Ring-Opening Sequence

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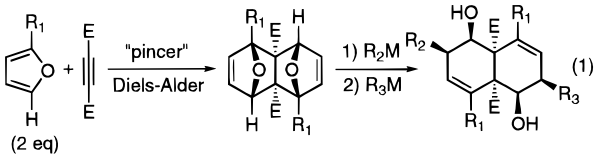
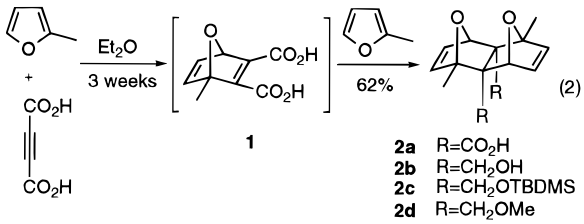
Tandem Diels−Alder cycloadditions efficiently construct multiple carbon−carbon bonds while generating complex polycyclic structures in a single chemical step.[1] For example, the "pincer" Diels−Alder served as a cornerstone in Paquette's classic synthesis of dodecahedrane.[2] However, the synthetic utility of the "pincer" Diels−Alder reaction remains underutilized in organic synthesis.

We considered that the "pincer" cycloaddition with furan as the diene component would provide rapid access to dioxacycloadducts that may be useful in the synthesis of complex natural products.[3] Thus, we envisioned combining the construction of dioxacyclic compounds with our recently reported methods of ring-opening reactions of oxabicyclic[2.2.1] systems as an efficient entry into a variety of polycyclic compounds bearing multiple stereocenters.[4,5] We now report the chemo-, stereo-, and regioselective synthesis of substituted dioxacyclic compounds via the inter- and intramolecular "pincer" Diels−Alder reaction and describe their subsequent stereo- and regioselective ring opening reactions (eq 1).

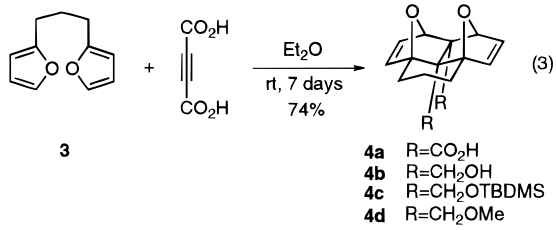


Our first priority was to determine the regiochemistry in the Diels−Alder cycloaddition starting from substituted furans. When a solution of acetylenedicarboxylic acid and 2 equiv of 2-methylfuran in ether was allowed to stand for 3 weeks at room temperature, the "pincer" cycloadduct **2a** slowly crystallized out of the solution, eq 2.[3g] The only product obtained of the 16 possible isomers



was identified as the C_2 symmetrical *exo-exo*[6] adduct **2a** in a 62% yield. The adduct had the two methyl groups in an "*anti*" relationship as proven by ^{13}C NMR. *To the best of our knowledge, this is the first example of a regioselective pincer Diels−Alder reaction.* The source of the regioselectivity may be steric in origin resulting from severe steric repulsion between the methyl group on the oxanorbornadiene **1** and the methyl group on the incoming 2-methylfuran, which strongly favors the "*anti*" product. The stereoselectivity (*exo vs endo*) is driven by crystal packing forces that cause selective crystallization of the symmetrical *exo-exo* product **2a**,[7a,b] whereas the chemoselectivity of 2-methylfuran toward the tetrasubstituted olefin of the ambient dienophile **1** is due to kinetic control in the multistage Diels−Alder reaction.[7c] In a single step, two new rings, four C−C bonds, and six stereocenters are formed.

In order to obtain information on the ring opening of the isomeric substrates with "*syn*" substituents, the furan components were linked by a three-carbon tether[8] and reacted with acetylenedicarboxylic acid. Reaction of **3** was significantly faster than with 2-methylfuran to provide the *exo-exo* dioxapentacyclic adduct **4a** in 74% yield after 1 week at room temperature, eq 3. None of the other seven possible isomers was observed.[9]



Prior to the ring-opening studies, the substrates were first reduced with $LiAlH(OMe)_3$ to the diols (**2b** and **4b**),

(1) The terms pincer, tandem, and domino have been used to describe multistage Diels−Alder reactions. For examples, see recent reviews on Diels−Alder cycloadditions: (a) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992.

(2) (a) For the first use of the term "pincer" Diels−Alder, see: Paquette, L. A.; Wyvratt, M. J.; Berk, H. C., Moerck, R. E. *J. Am. Chem. Soc.* **1978**, *100*, 5845. (b) Paquette, L. A.; Balogh, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 774.

(3) (a) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1931**, *490*, 243. (b) Diels, O.; Olsen, S. *J. Prakt. Chem.* **1940**, *156*, 285. (c) Stockman, H. *J. Org. Chem.* **1961**, *26*, 2025. (d) Cram, D. J.; Knox, G. R. *J. Am. Chem. Soc.* **1961**, *83*, 2204. (e) Weis, C. D. *J. Org. Chem.* **1963**, *28*, 74. (f) Cram, D. J.; Montgomery, C. S.; Knox, G. R. *J. Am. Chem. Soc.* **1966**, *88*, 515. (g) Kallos, J.; Deslongchamps, P. *Can. J. Chem.* **1966**, *44*, 1239. (h) Gelin, R.; Debard, A. *Bull. Soc. Chim. Fr.* **1966**, 144. (i) Gandhi, R. P.; Chadha, V. K. J. *Chem. Soc., Chem. Commun.* **1968**, 552. (j) For historical information on this reaction, see: Slee, J. D.; LeGoff, E. *J. Org. Chem.* **1970**, *35*, 3897. (k) McCulloch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1974**, *52*, 1013. (l) McCulloch, A. W.; McInnes, A. G. *Can. J. Chem.* **1975**, *53*, 1496. (m) Weber, G.; Menke, K.; Hopf, H. *Chem. Ber.* **1980**, *113*, 531. (n) Maier, G.; Jung, W. A. *Tetrahedron Lett.* **1980**, *21*, 3875. (o) Hall, R. H.; Harkema, S.; den Hertog, H. J.; van Hummel, G. J.; Reinhoudt, D. N. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 312. (p) Maier, G.; Jung, W. A. *Chem. Ber.* **1982**, *115*, 804. (q) Jurczak, J.; Belniak, S.; Kozluk, T.; Pikul, S.; Salanski, P. *Bull. Pol. Acad. Sci., Chem.* **1984**, *32*, 135. (r) Russell, R. A.; Longmore, R. W.; Weerasuria, K. D. V.; Warrener, R. N. *Aust. J. Chem.* **1991**, *44*, 1341. (s) During the course of our study, the synthesis of a dioxapentacycle by a simultaneous double Diels−Alder addition of a tethered bis-furan with a bis-dienophile has been reported; see: Marchionni, C.; Vogel, P.; Roversi, P. *Tetrahedron Lett.* **1996**, *37*, 4149.

(4) (a) For a recent review on the ring opening of oxabicyclic systems, see: Woo, S.; Keay, B. *Synthesis* **1996**, 669. (b) For a review of our previous work and historical information on this reaction, see: Lautens, M. *Synlett* **1993**, 177. (c) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532.

(5) For a recent review on aromatic heterocycles as intermediates in synthesis, see: Shipman, M. *Contemp. Org. Synth.* **1995**, *2*, 1.

(6) Some authors refer to this stereochemistry as *endo-endo.*

(7) (a) No trace of the "*syn*" dimethyl cycloadduct was observed. However, ^1H NMR spectrum of the mother liquor indicated the presence of the *exo-endo* cycloadduct, which did not crystallize out of the solution. The oxanorbornadiene type intermediate **1** was the major component present in the reaction mixture. (b) For a detailed study on the Diels−Alder reaction between furan and dimethyl acetylenedicarboxylate, see: McCulloch, A. W.; Smith, D. G.; McInnes, A. G. *Can. J. Chem.* **1973**, *51*, 4125. (c) Visnick, M.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1621.

(8) The bis-furan **3** was prepared in 38% yield by treating 1,3-diiodopropane with 2-lithiofuran.

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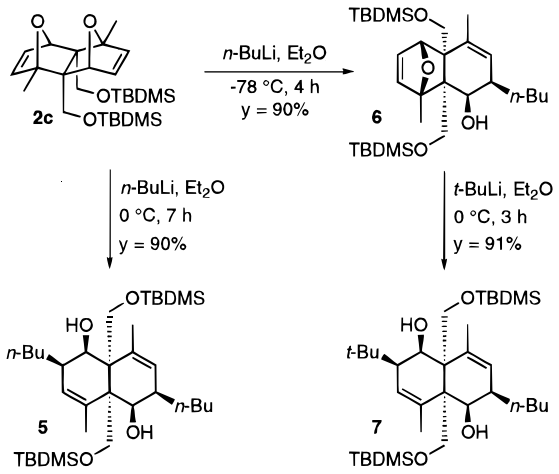
Scheme 1



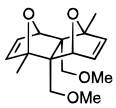
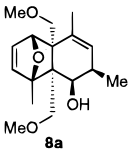
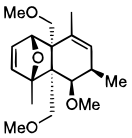
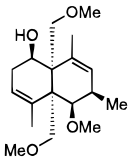
which were protected as disilyl (**2c** and **4c**) or dimethyl ethers (**2d** and **4d**).

The feasibility of the ring-opening reaction was first explored with the dioxatetracycle **2c** (Scheme 1). When **2c** was treated with excess *n*-BuLi at 0 °C for 7 h, the decalin **5** bearing six stereocenters was obtained in 90% yield. The attack of the incoming nucleophile occurred exclusively on the endo face of the substrate at the positions distal to the bridgehead substituent.[4a,b] *The most useful feature of the reactivity of the dioxacyclic compounds is that the first ring-opening reaction is significantly faster than the second.* Indeed, the mono ring opening was easily achieved by simply performing the reaction at lower temperature. Thus, treatment of **2c** at −78 °C for 4 h with 5 equiv of *n*-BuLi provided the mono ring-opened product **6** in 90% yield. The subsequent reaction of **6** with *t*-BuLi gave the nonsymmetrical decalin **7**.

MeLi, which usually fails to react with bridgehead substituted oxabicyclo[2.2.1] systems, was shown to induce the first opening on the dioxatetracycle **2d** (entry 1, Table 1). Hydridic opening was also readily achieved. A reductive ring opening of **8b** using the nickel-catalyzed hydroalumination−β-elimination reaction developed in our laboratories[4c] yielded the decalin **9** in 78% yield, entry 2.[10]

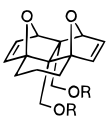
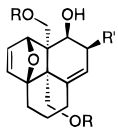
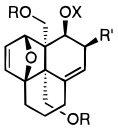
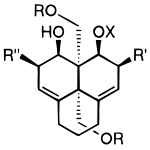
We also investigated the reactivity of dioxapentacyclic compounds in ring-opening reactions. A different reactivity profile was observed as summarized in Table 2. Careful control of the reaction temperature led to the mono ring opening of **4c** using *n*-BuLi in excellent yield (Table 2, entry 1). MeLi also induced the mono ring opening of **4d**, although in modest yield (Table 2, entry 2). However, **4c** failed to undergo double opening to **12** regardless of the reaction temperature or the number of equivalents of *n*-BuLi; instead it led mostly to decomposition. In order to increase the reactivity of **10** toward the second opening, a more Lewis acidic metal counterion was added. Thus, **10** was treated with 2 equiv of *n*-BuMgCl followed by 5 equiv of *n*-BuLi to cleanly provide the bis-opened product **12** (Table 2, entry 3). These conditions were also successful for the ring opening of **10** with *t*-BuLi to yield **13** (Table 2, entry 4). Finally, we briefly investigated the reductive ring opening of **11b** using Ni(COD)$_2$/DIBAL-H, which gave **14** in 72% yield (Table 2, entry 5).[10]

Table 1. Dioxatetracycle Ring Opening

Entry	Substrate	Product	Yield[a]
1	 **2d**	 **8a**	40%[b]
2	 **8b**[c]	 **9**	78%[d]

[a] Isolated yield of analytically pure product. [b] MeLi (5 equiv) was added to a solution of **2d** in Et$_2$O, and the mixture was stirred for 24 h at rt. [c] The alcohol **8a** was protected as its methyl ether by treatment with KH followed by MeI and 18-crown-6 to give **8b** in 92% yield. [d] DIBAL-H (1.1 equiv) was added over 1 h to a solution of **8b**, Ni(COD)$_2$ (19 mol %), and 1,4-bis(diphenylphosphino)butane (38 mol %) in toluene.

Table 2. Dioxapentacycle Ring Opening

Entry	Substrate	Product	Yield[a]
1	 **4c** R=TBDMS	 **10** R'=*n*-Bu	97%[b]
2	**4d** R=Me	**11a** R'=Me	41%[c]
3	 **10** R=TBDMS R'=*n*-Bu X=H	 **12** R''=*n*-Bu	78%[d]
4	**10** R=TBDMS R'=*n*-Bu X=H	**13** R''=*t*-Bu	84%[e]
5	**11b**[f] R=Me R'=Me X=Me	**14** R''=H	72%[g]

[a] Isolated yield of analytically pure product. [b] *n*-BuLi (5 equiv) was added to a solution of **4c** in Et$_2$O, and the mixture was stirred for 24 h at −78 °C. [c] MeLi (5 equiv) was added to a solution of **4d** in Et$_2$O, and the mixture was stirred for 24 h at rt. [d] A solution of **10** in Et$_2$O was treated with *n*-BuMgCl (2 equiv) followed by *n*-BuLi (5 equiv) and THF, and the mixture was stirred for 12 h at rt. [e] A solution of **10** in Et$_2$O was treated with *t*-BuMgCl (2 equiv) followed by *t*-BuLi (5 equiv), and the mixture was stirred for 8 h at rt. [f] The alcohol **11a** was protected as its methyl ether by a treatment with KH followed by MeI and 18-crown-6 to give **11b** in 92% yield. [g] DIBAL-H (1.1 equiv) was added over 8 h to a solution of **11b**, Ni(COD)$_2$ (12 mol %), and 1,4-bis(diphenylphosphino)butane (24 mol %) in toluene. After the addition was complete, the mixture was stirred for an additional 12 h at rt.

In summary, we have developed a simple and flexible strategy for the rapid assembly of decalins, and we are currently defining the scope and limitations of this methodology.

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Supporting Information Available: Experimental details and characterization are available for all compounds (11 pages).

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(9) ^{1}H NMR spectrum of the mother liquor showed the absence of the oxanorbonadiene intermediate, which suggests that the rate of the intramolecular cycloaddition is much faster than the intermolecular one. Also, no trace of the *exo-endo* cycloadduct was observed in the reaction mixture.

(10) The hydroxy group had to be protected in order for the reductive ring-opening reaction to occur.