actions that must accompany the endo cycloaddition. This substantial increase in the observed pressure-induced diastereoselectivity must then be attributed to the additional difference in the volume of activation between the reaction paths leading to the endo and exo diastereomers due to the additional dienophile C-2 cis substituent.

The cycloadducts **4** and **7** were converted into the complementary series of carbohydrates through implementation of one of two established[18,19] two-step reaction sequences. Catalytic hydrogenation of **4** and **7** followed by lithium aluminum hydride reduction provided 2,4-dideoxymannopyranoside **3a** and 4-deoxymannopyranoside **3c**, respectively, as the exclusive reaction products, Scheme II. Hydrogen delivery in the catalytic hydrogenation of **4** and **7** occurs from the α-face, anti to the proximal C-4 methoxy substituent and distal C-2/C-3 substituents, and provides **5** and **8** in which the C-6 methoxycarbonyl groups occupy a stable equatorial position. Alternatively, lithium aluminum hydride reaction of **4** and **7** and acetylation of the resulting alcohols followed by stereoselective hydroboration–oxidation provided 4-deoxymannopyranoside **3b** and mannopyranoside **3d**,[20] respectively. The predictably regiospecific hydroboration proceeds from the α-face, anti to the proximal C-4 methoxy substituent, in agreement with prior observations.[13,26,27]

The readily accessible dienophile **2b**,[12] which has proven convenient to secure on a preparative scale, and its demonstrated capabilities for productive participation in regiospecific, endo-selective inverse electron demand Diels–Alder reactions should prove to be of general synthetic utility in the diastereoselective preparation of selectively protected cyclic *cis*-1,2-diols. The pressure-promoted [4 + 2] cycloaddition reactions of β,γ-unsaturated α-keto ester **1** with dienophiles **2a** and **2b** provided productive, regiospecific endo-selective $LUMO_{diene}$-controlled [4 + 2] cycloadditions suitable for the divergent, de novo synthesis of fully functionalized and selectively protected carbohydrates. The continued exploration of the [4 + 2] cycloaddition reactions of β,γ-unsaturated α-keto esters and their applications are in progress and will be reported in due course.

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Supplementary Material Available: Experimental procedures and full spectral and physical characterization of **2b**, **3a–d**, and **4–9** (15 pages). Ordering information is given on any current masthead page.

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Diels–Alder Reactions of α-Oxy-*o*-xylylenes†

Summary: Treatment of benzocyclobutenols or their acetates with *n*-butyllithium at 0 °C or less can generate the corresponding α-oxy-*o*-xylylenes, which can then undergo Diels–Alder reactions.

Sir: The formation of the reactive but elusive *o*-xylylenes (5,6-bis(methylene)-1,3-cyclohexadienes) followed by their Diels-Alder reactions constitutes a powerful synthetic sequence for the construction of many cyclic natural products.[1] However, the typical temperatures (>25 °C) employed for this sequence have frequently been dictated by the rates at which the initial *o*-xylylene can be formed from its various stable precursors.[2] Since electron-donating groups at sp^3 carbons of a benzocyclobutenyl ring lower the energy barriers toward xylylene formation,[3] we surmise that α-anionic centers at those sp^3 carbons could further lower the temperature (<0 °C) for the thermal electrocyclic ring opening[4] and that the associated cation M of the resulting *o*-xylylene could then behave as a Lewis acid center for a succeeding Diels–Alder reaction at the same temperature. This hypothetical sequence has been realized with dimethyl maleate (**7**), dimethyl fumarate (**8**), and γ-crotonolactone (**9**) as dienophiles (see Scheme I).

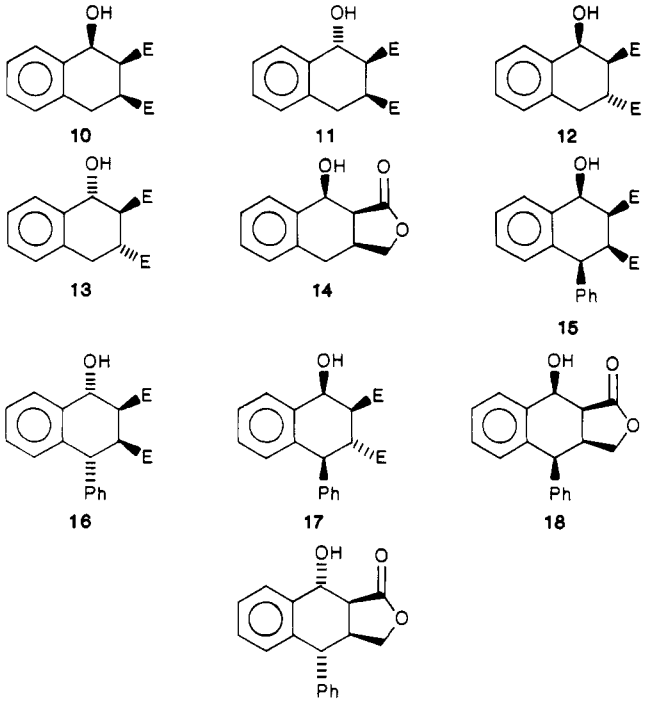
Typical Experimental Procedure (Method A, M = Li). To a cooled (−78 °C), dry 0.05 M THF solution of substrate **1**[5a] or **2**[5b] was added dropwise *n*-BuLi in hexane (1.1 equiv for alcohols or 2.2 equiv for acetates). After stirring at −78 °C for 30 min, dienophile (2 equiv) was added (neat for **7** and **9** or concentrated THF solution for **8**) dropwise and the resulting mix was allowed to stir at the temperature and time shown in Table I. The following observations were noted: First the solutions of these presumed oxy-*o*-xylylenes (M = Li) are colored. While the deep magenta color of **6** instantly appears after the addition of *n*-BuLi at −78 °C, the burgundy red color of **5** slowly appears after warming to −25 °C in the absence of dienophiles.[6a] Second, without added dienophiles, the color of **6** appears to persist for hours at −78 °C, while that of **5** slowly fades at 0 °C, thus indicating the instability of **5** toward other modes of decomposition near the temperature of its formation. Lastly, addition of relatively unreactive **9**[6b] would discharge both of these colors within seconds even in the case where the colored solution of **5** was cooled to −78 °C. The resulting mix was quenched at −78 °C with saturated aqueous NH_4Cl solution and extracted with Et_2O. The organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The adducts shown in Table I[7] were separated from the

(18) Moe, O. A.; Warner, D. T.; Buckley, M. I. *J. Am. Chem. Soc.* **1951**, *73*, 1062.
(19) (a) Micovic, M. V.; Mihailovic, M. LJ. *J. Org. Chem.* **1953**, *18*, 1190. (b) Hochstein, F. A.; Brown, W. G. *J. Am. Chem. Soc.* **1948**, *70*, 3484.
(20) The confirmed assignment of stereochemistry for mannopyranoside **3d** is based on a ^1H NMR comparison with 4,6-di-*O*-acetyl-3-*O*-carbamoyl-1,2-*O*-(1-ethoxyethylidene)-β-D-mannopyranose,[21] in which the following coupling constants have been reported: $J_{2,3}$ = 3.9, $J_{3,4}$ = 10.0, $J_{4,5}$ = 9.7, $J_{5,6A}$ = 12.4, 2.5, $J_{5,6B}$ = 12.4, 4.8 Hz. The coupling constants for **3d**: $J_{2,3}$ = 3.5, $J_{3,4}$ = 9.4, $J_{4,5}$ = 9.4, $J_{5,6A}$ = 11.8, 3.6, $J_{5,6B}$ = 11.8, 5.5 Hz. In addition, the chemical shift and multiplicity of H-2 (**3d**) correlate well with those reported for H-2 in methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside[22] (5.61 ppm, 1 H, br d; versus 5.35, 1 H, t, $J_{1,2}$ = $J_{2,3}$ = 2 Hz, for α-D-mannopyranoside). For **3d**: H-2, 5.54 ppm, 1 H, d, $J_{2,3}$ = 3.5 Hz. The C-1 (anomeric) stereochemistry of **3d** was further confirmed by ^{13}C NMR, which showed a signal for C-1 at 97.70 ppm with $^1J_{CH}$ = 155.0 Hz in good agreement with the observations of Bock and Pedersen. ($^1J_{CHax}$ = 155.9 Hz, $^1J_{CHeq}$ = 170.6 Hz).[22-25]
(21) Millar, A.; Kim, H. P.; Minster, D. K.; Ohgi, T.; Hecht, S. M. *J. Org. Chem.* **1986**, *51*, 189.
(22) Ogawa, T.; Katano, K.; Sasajima, K.; Matsui, M. *Tetrahedron* **1981**, *37*, 2779.
(23) Bock, K.; Lundt, I.; Pedersen, C. *Tetrahedron Lett.* **1973**, 1037.
(24) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkins Trans. 2* **1974**, 293.
(25) Bock, K.; Pedersen, C. *Acta Chem. Scand., Ser B* **1975**, *B29*, 258.
(26) Anselmi, C.; Catelani, G.; Monti, L. *Gazz. Chim. Ital.* **1983**, *113*, 167.
(27) Barili, P. L.; Berti, G.; Catelani, G.; Colonna, F.; Mastrorilli, E. *J. Chem. Soc., Chem. Commun.* **1986**, 7.
(28) National Institutes of Health research career development award recipient, 1983–1988 (CA 01134); Alfred P. Sloan research fellow, 1985–1989.

† This communication is dedicated to Professor Satoru Masamune on the occasion of his 60th birthday.

0022-3263/88/1953-5796$01.50/0

Table I



entry	substr	dienophile	method (h, °C)	rel ratio of adducts (%)	yield, %
1[8a,b]	1a	7	B (12, 110)	10 (20), 11 (80)	31
2[9]	1a	8	B (12, 110)	12 (60), 13 (40)	86
3[8b,c]	1a	9	B (24, 110)	14 (100)	11
4[10]	1a	7	A (1, 0)	10 (60), 11 (17), 12 (19), 13 (4)	55
5	1a	8	A (1, 0)	12 (87), 13 (13)	76
6[11]	1a	9	A (1, 0)	14 (100)	46
7[8a,10]	1b	7	A (1, 0)	10 (67), 11 (10), 12 (17), 13 (6)	32
8	1b	8	A (1, 0)	12 (82), 13 (18)	74
9[11]	1b	9	A (1, 0)	14 (100)	38
10[12]	2b	7	B (5, 180)	15 (30), 16 (70)	61
11[12]	2b	8	B (5, 140)	17 (100)	90
12	2b	7	A (0.5, −78)	15 (40), 16 (60)	58
13	2b	8	A (0.5, −78)	17 (100)	57
14[13]	2b	9	A (0.5, −78)	18 (72), 19 (20)	76

crude residue by preparative TLC on silica with multiple developments using EtOAc/hexane mixture (1/5) as eluent. The results along with those obtained from the purely thermal reactions of **1a** and **2b** in toluene with dienophiles (method B, M = H or Ac) are tabulated below (see Table I).

Several notable features are evidenced in the Table I: First, the temperatures and sequence times for comparable adduct formation are substantially lower when using method A than method B, thus inferring the powerful electron-donating effect of the oxyanionic center in opening the cyclobutenyl rings to *o*-xylylenes **5** and **6**. Second, the combination of the lower temperature and the Li cation significantly increase the endo selectivity.[14] While the degrees of the enhancement are small in entries 2 vs 5 and 10 vs 12, the endo/exo ratio of the respective adducts **10** and **11** in entry 4 in nearly inverted from that in entry 1. Third, while the yields from **1b** using method A are slightly lower than that from **1a** using the same method, the product distributions are similar, thus suggesting that their Diels–Alder reactions evolve from the same *o*-xylylene **5**. As a consequence, the acetate may be of synthetic advantage in some cases where the benzocyclobutenols are extremely prone to tautomerize to the corresponding ortho-substituted benzaldehydes. For example, in the attempt to prepare **2a** from **2b** by acid-catalyzed methanolysis[15a] at 0 °C, a 5/1 mixture of **2a** and *o*-benzylbenzaldehyde was respectively formed. The attempted sepa-

(1) For recent reviews: (a) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. (b) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 85 and references therein.

(2) (a) For an example of a thermal *o*-xylylene formation as the rate-determining step in the sequence starting from benzocyclobutenol, see: Arnold, B. J.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. I* **1974**, 409. (b) For an example where a photoinitiated sequence can be conducted near 0 °C, see: Hornback, J. M.; Barrows, R. D. *J. Org. Chem.* **1983**, *48*, 90.

(3) Oppolzer, W. *Synthesis* **1978**, 793.

(4) (a) For a possible rationale for the bond-breaking process enhanced by α-oxy anionic centers as in oxy-Cope reactions, see: (a) Evans, D. A.; Baillargeon D. J. *Tetrahedron Lett.* **1978**, 3319. (b) Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994 and references therein. (c) For an example for an α-anion driven electrocyclic opening of cyclobutene at low temperature, see: Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. *Ibid*, **1981**, *103*, 1256.

(5) (a) Preparation of **1a** and **1b**: Bubb, W. A.; Sternhell, S. *Aust. J. Chem.* **1976**, *29*, 1685. (b) Preparation of **2b**, which starts from *o*-benzylbenzaldehyde: Charlton, J. L.; Alauddin, M. M.; Penner, G. H. *Can. J. Chem.* **1986**, *64*, 793.

(6) (a) For comparison: **5** (M = H) has λ_{max}(Xe matrix) = 393 nm [Gebicki, J.; Krantz, A. *J. Chem. Soc., Perkin Trans. II* **1984**, 1623]. (b) Block, E.; Stevenson, R. *J. Chem. Soc., Perkin Trans. I* **1973**, 308.

(7) The regio- and relative stereochemical identification of adducts were made thru correlation with known compounds or analysis of 200-MHz ^{1}H NMr spectra. See supplementary material.

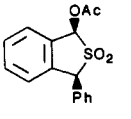
(8) (a) Under the reaction conditions, the indicated endo **10** was isolated in the form of its known γ-lactone [Arnold, B. J.; Mellows, S. M.; Sammes, P. G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 401]. (b) Small amounts of *o*-tolualdehyde were observed in these reactions. Also see ref 2a. (c) Adduct **14** was identical with that in ref 8a.

(9) The indicated exo adduct **13** can be refluxed in xylenes to form a γ-lactone [mp ($CHCl_3$/Et_2O) 170–171.5 °C; IR ($CHCl_3$) 1785 and 1745 cm^{-1}]. HRMS (*m/e*): 232.0733 [calcd for $C_{13}H_{12}O_4$, 232.0736]. See supplementary material for further data.

(10) (a) The formation of **12** and **13** presumably arose thru epimerization or a retroaldol and realdol sequence of **10** and **11** under the reaction conditions. Also, a referee has suggested that **8** arising from a partial isomerization of **7** could then react to give **12** and **13**. (b) The percent of **10** also includes the amount of γ-lactone which is partially formed from **10**.

(11) δ-Lactols (30–40%) were also isolated and presumably arose thru hetero-Diels–Alder reactions between **5** and *o*-tolualdehyde, which in turn came from an acid–base reaction with **9**. Oxidation of these lactols with pyridinium chlorochromate led to the known 3,4-dihydro-3-(2-methylphenyl)-1*H*-2-benzopyran-1-one [Ashby, E. C.; Coleman, D.; Gamasa, M. *J. Org. Chem.* **1987**, *52*, 4079].

(12) The data were abstracted from ref 5b and the direct products are the *acetates* of the alcohols shown in Table I. Although the authors there started with the cis sulfone i, they also isolated **2b** along with some of their adducts. They were able to show that **2b** also yields adducts near the same conditions as their sulfones as we suggest in Table I. However, in either precursor as the source of xylylene **6** (M = Ac), the intent of the comparison in Table I is to illustrate the differences between methods A and B in terms of the reaction conditions and endo/exo selections in the formation of their corresponding products. Also in ref 5b, calculations there showed the plane of the phenyl ring is rotated 60° from the plane of the xylylene frame.

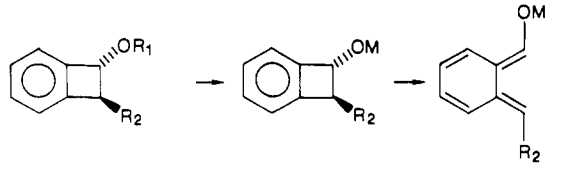


i

(13) The relative stereochemistry of the remaining adduct (8%) is yet to be assigned. However its regiochemistry is the same as that of **19** since both of these compounds yield the same ene–lactone [IR (neat) 1755, 1665 cm^{-1}] upon treatment with camphorsulfonic acid in refluxing toluene. Further spectral data are in the supplementary material.

(14) (a) For a systematic study on the effect of temperature and catalyst on endo selection, see: Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 731. (b) The increased endo selectivity due to the added Lewis acid complexing the carbonyl oxygen of the enone has been rationalized as the change in the LUMO of the dienophile for the Diels–Alder reaction: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; J. Wiley and Sons: New York, 1976; pp 161–165.

Scheme I



1a (R_1 = H, R_2 = H) **3** (R_2 = H) **5** (R_2 = H)
1b (R_1 = Ac, R_2 = H)
2a (R_1 = H, R_2 = Ph) **4** (R_2 = Ph) **6** (R_2 = Ph)
2b (R_1 = Ac, R_2 = Ph)

5 or 6 + dienophile ⟶ Diels-Alder adducts

ration of this mix by silica gel chromatography led to the complete destruction of **2a**.[15b,c]

Finally, the entire sequence in Scheme I can be initiated with other reagents aside from *n*-BuLi. However, the associated cation M of these reagents plays a significant role in the rate of *o*-xylylene formation and/or product distribution in the subsequent Diels–Alder reaction. For example, deprotonation of **1a** with MeMgBr at 0 °C followed by addition of **7** at 25 °C provides adducts [relative % ratio: **10** (48), **11** (21), **12** (21), **13** (10)] in 60% yield after 12 h/25 °C.[16,17] Reduction of **2b** with *i*-Bu_2AlH (2.2 equiv, 1 h, 0 °C) followed by addition of **7** gave a 3:1 mixture (60%) of **15**[18] and **16**, respectively, after 12 h at 25 °C. While this last reductively initiated sequence proceeded at a much higher temperature and at a longer time than that of method A (entry 12), the major adduct is now endo.[14b]

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Supplementary Material Available: Assignments of adducts shown in Scheme I (4 pages). Ordering information is given on any current masthead page.

(15) (a) MacDonald, D. I.; Durst, T. *Tetrahedron Lett.* **1986**, *27*, 2235. (b) The crude mixture which contains **2a** has the following spectra: IR (neat) 3400 cm^{-1}; ^1H NMR ($CDCl_3/D_2O$, δ) 7.0–8.0 (m, 9 H), 4.98 (d, J = 1.5 Hz, 1 H), 4.45 (s, 1 H). (c) After submission of this manuscript, the instabilities of **2a** and its analogues were also noted by: Macdonald, D. I.; Durst, T. *J. Org. Chem.* **1988**, *53*, 3663.

(16) (a) Grignard reactions of benzocyclobutenone afford of tertiary alcohols, which can then be opened by NaOMe to give *o*-methylphenyl ketones [Horner, L.; Subramaniam, P. V.; Eiben, K. *Liebigs Ann. Chem.* **1968**, *714*, 91]. (b) When the aromatic rings of **4** are heavily substituted with ethereal oxygenated groups and with M = MgBr, the corresponding *o*-benzylbenzaldehyde derivative was formed in the absence of dienophile [Jung, M. E.; Lam, P. Y.-S.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087]. Here Jung has invoked the intermediacy of an *o*-formylbenzhydryl anion, which might suggest that our Diels–Alder adducts could also arise thru a Michael followed by an aldol reaction sequence.

(17) Adducts **10** and **13** form their corresponding γ-lactones under the reaction conditions.

(18) Under the reaction conditions, adduct **15** forms its known γ-lactone [see ref 8a].

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