d, J = 11.3 Hz, $COCH_2Ph$), 4.85 (1 H, d, J = 11.3 Hz, $COCH_2Ph$), 5.05 and 5.08 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph), 5.11 and 5.13 (2 H, AB q, J_{AB} = 12.4 Hz, CO_2CH_2Ph). Anal. Calcd for $C_{25}H_{23}O_5N_3$: C, 67.4; H, 5.20. Found: C, 67.4; H, 5.12.

Dibenzyl L-*erythro*-β-(Benzyloxy)aspartate (6). Hydrogen sulfide was led into a solution of **5** (400 mg, 0.90 mmol) and triethylamine (0.2 mL) in CH_2Cl_2 (20 mL) at room temperature.[12] After 4 h the solution was washed with water (10 mL), brine (10 mL), and aqueous sodium hydrogen carbonate (10 mL), then dried, and concentrated. Column chromatography (SiO_2, 1:3 EtOAc–hexane and then EtOAc) gave **6** (0.303 g, 80%) as a syrup with $[\alpha]^{20}_D$ +35.6° (*c* 1.0, EtOAc); IR (neat) 3400 (NH_2), 1750 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (1 H, d, J = 3.8 Hz, HC(α)), 4.31 (1 H, d, J = 3.8 Hz, HC(β)), 4.48 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.84 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 5.01 and 5.08 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph), 5.06 (2 H, s, CO_2CH_2Ph). Anal. Calcd for $C_{25}H_{25}O_5N$: C, 71.6; H, 6.01; N, 3.34. Found: C, 72.3; H, 6.10; N, 3.38.

β-Benzyl L-*erythro*-β-(Benzyloxy)aspartate (7). Aqueous potassium hydroxide (0.25 M, 3.6 mL, 0.90 mmol) was added over a period of 3 h to a solution of **6** (380 mg, 0.91 mmol) and potassium iodide (150 mg, 0.90 mmol) in acetone–water (25:2, 54 mL) at −20 °C. After an additional 30 min, the solution was allowed to attain room temperature and the acetone was evaporated. The resulting aqueous phase was extracted with EtOAc (3 × 30 mL), from which **6** (202 mg) was recovered. Addition of aqueous acetic acid (0.125 M, 7.2 mL) to the aqueous phase gave a precipitate of **7** (76 mg). Two further cycles of hydrolysis were applied to recovered **6**, yielding 37 mg of **7**. Column chromatography (SiO_2, 15:2:1 EtOAc–HOAc–water) of the combined filtrates gave 24 mg of **7**, providing a total of 137 mg (46%) of crystalline **7** with mp 182–184 °C:$[\alpha]^{20}_D$ +49.1° (*c* 0.8, Me_2SO); IR (KBr) 3700–2100 (CO_2H, NH_2), 1760 (ester C=O) cm^{-1}; ^1H NMR (CD_3OD) δ 4.05 (1 H, d, J = 3.6 Hz, HC (α/β)), 4.54 (1 H, d, J = 3.6 Hz, HC (α/β)), 4.62 (1 H, d, J = 11.2 Hz, $COCH_2Ph$), 4.82 (1 H, d, J = 11.2 Hz, $COCH_2Ph$), 5.18 and 5.26 (2 H, AB q, J_{AB} = 12.2 Hz, CO_2CH_2Ph). Anal. Calcd for $C_{18}H_{19}O_5N$: C, 65.6; H, 5.81; N, 4.25. Found: C, 65.8; H, 5.82; N, 4.19.

β-Benzyl *N*-(*tert*-Butoxycarbonyl)-L-*erythro*-β-(benzyloxy)aspartate (8). Triethylamine (81 mg, 0.80 mmol) and di-*tert*-butyl dicarbonate (175 mg, 0.80 mmol) were added to a suspension of **7** (246 mg, 0.80 mmol) in DMF (9 mL). After 1 h, EtOAc (9 mL) and water (16 mL, acidified to pH 1–2 with aqueous 1 M $KHSO_4$) were added. The aqueous phase was extracted with EtOAc (9 mL), and the combined organic phases were dried and concentrated. Column chromatography (SiO_2, 1:1 EtOAc–hexane) of the residue gave **8** (246 mg, 71%) as a syrup with $[\alpha]^{20}_D$ +74.7° (*c* 1.0, EtOAc): IR (KBr) 3700–2400 (CO_2H, NH); ^1H NMR (acetone-d_6) δ 1.39 (9 H, s, Me_3C), 4.46 (1 H, d, J = 3.2 Hz, HC(β)), 4.60 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.84 (1 H, d, J = 11.5 Hz, $COCH_2Ph$), 4.86 (1 H, m, HC (α)), 5.24 (2 H, s, CO_2CH_2Ph), 6.00 (1 H, br d, NH). Anal. Calcd for $C_{23}H_{27}O_6N$: C, 64.3; H, 6.34; N, 3.26. Found: C, 64.2; H, 6.49; N, 3.14.

Acknowledgment. We thank Prof. Johan Stenflo and Dr. Per Fernlund (Department of Clinical Chemistry, Malmö General Hospital) for suggesting this work, Prof. Börje Wickberg for his interest, and the Swedish Medical Research Council (Project B85-03X-04487-11Z) for financial support.

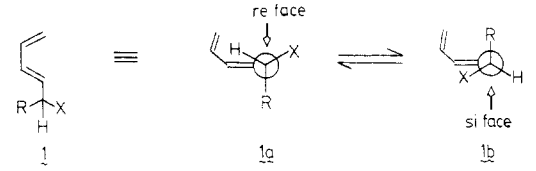
Registry No. 1, 87-69-4; 2, 622-00-4; 3, 103710-70-9; 4, 103710-71-0; 5, 103694-08-2; 6, 103694-09-3; 7, 103694-10-6; 8, 103694-11-7; benzyl trichloroacetimidate, 81927-55-1; trifluoromethanesulfonic anhydride, 358-23-6; di-*tert*-butyl dicarbonate, 24424-99-5.

Communications

Direct β-Lithiation of 2-Alkoxy Dienes: Use in an Asymmetric Diels–Alder Reaction

Summary: Aldehydes react with β-lithiated 2-alkoxy dienes, obtained via direct deprotonation, to produce a class of asymmetric dienes which exhibit complete face selectivity in the intermolecular Diels–Alder reaction.

Sir: Asymmetric Diels–Alder reactions involving chiral dienes have begun to attract attention.[1,2] More specifically chemists have been interested in determining the effect an adjacent chiral center has on the diastereoselectivity of the Diels–Alder reaction.[2,3] As illustrated in structure **1**, the adjacent chiral center is most often substituted with an alkyl group (R), a heteroatom (X), and a hydrogen. In accord with recently proposed perpendicular models[4] for electrophilic attack on chiral allyl or dienyl systems, the reactive conformers can be depicted as either **1a** or **1b**, both of which place the alkyl group (R) in the plane of the π-system. While intuitively one would then prefer to place the bulkier heteroatom away from the dienyl system (i.e., **1a**), recent calculations have shown that electronic factors tend to favor the conformer **1b** with the "inside" heteroatom.[4b,5] Experimental results for the Diels–Alder reaction are conflicting as products arising from both conformer **1a** (X = OR)[2a,b] and **1b** (X = NR^1R^2)[2c] have been reported. Furthermore no dienyl system related to structure **1** has yet to exhibit complete π-face selectivity in the intermolecular Diels–Alder reaction.[3,18] In this paper we wish to report on the synthesis of some novel diene structures (see **7–10**) that react with complete π-face selectivity apparently via conformer **1a**.



1 **1a** **1b**

We have recently described the direct β-lithiation of an enol ether (**2a** → **2b**).[6] In an effort to extent this methodology to synthetically more interesting examples we have

(1) For a review that contains the earlier examples, see: Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 8, pp 474–477.

(2) (a) Gree, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carrie, R. *Tetrahedron Lett.* **1984**, *25*, 3697. (b) Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187. (c) Kozikowski, A. P.; Nieduzak, T. R. *Tetrahedron Lett.* **1986**, *27*, 819.

(3) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421.

(4) (a) Houk, K. N.; Rondan, N. G.; Paddon-Row, M. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (c) McGarvey, G. T.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435. (d) Fleming, I.; Lewis, J. L. *J. Chem. Soc., Chem. Commun.* **1985**, 149.

(5) Kahn, S. D.; Hehre, W. J. *Tetrahedron Lett.* **1985**, *26*, 3647.

(6) McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, *25*, 5977.

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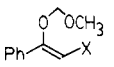
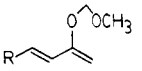
focused our attention on the substituted dienyl enol ethers **3** and **4**. While there were few reported preparations of



2a X=H
2b X=Li



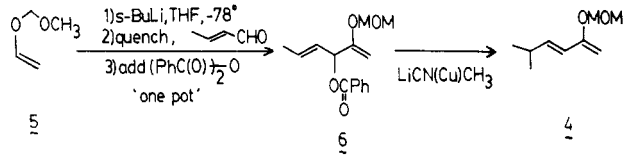
3 R=Ph
4 R=i-Pr

2-methoxymethyl (MOM) alkoxy dienes,[7] we have uncovered a number of expedient routes to such species including the sequence illustrated in Scheme I. Noteworthy here is the chemoselectivity of the cuprate addition to **6** in which the more electron-deficient allyl benzoate undergoes substitution.[8] In this fashion the (*E*)-diene **4** is prepared in a two-pot sequence from enol ether **5** (67% overall yield).[9]

The results of the directed β-lithiation of alkoxy dienes **3** and **4** are shown in Scheme II. In accord with our previous experience the best metalation conditions involve the use of *sec*-BuLi at −78° C in ethereal solvents. For these dienyl systems competing addition of the alkyllithium base to the diene[10] is a major side reaction which can be minimized by the use of DME as solvent.[11] Reaction of the resulting β-lithiated enol ethers with aldehydes produces the addition products **7–10** in moderate to good yield.[12,13] This is to our knowledge the first example of direct substitution onto a 2-alkoxy diene. The products are an interesting variant of a typical aldol product; that is, they are essentially enolized aldol products.[14] Furthermore the directed nature of the deprotonation reaction assures the exclusive production of the *Z* isomer. While such stereoselectivity had been inferred in our previous work,[6] the product resulting from the Diels–Alder reaction of diene **11** (vide infra) confirms the stereochemical assignment.[16] The stereochemical homogeneity of these dienes is essential for the successful utilization of these compounds in asymmetric synthetis.

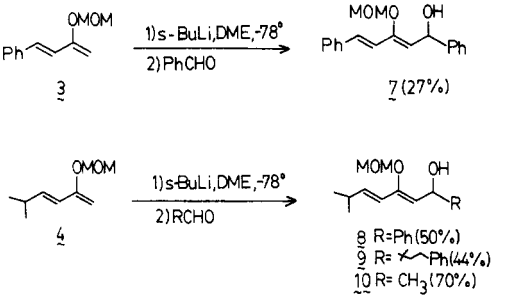
Alkoxy dienes are the premier dienes for the use in the Diels–Alder reaction. Hence it was of interest to compare the diastereoface selectivity of our novel diene structures,

Scheme I



5 **6** **4**

Scheme II

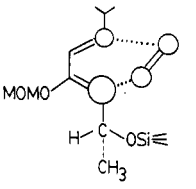


3 **7** (27%)

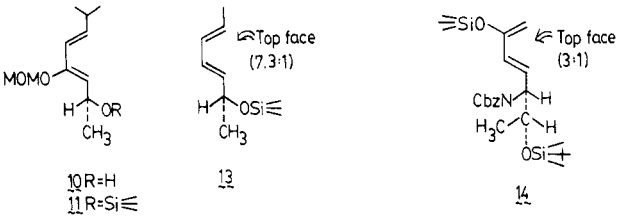
4

8 R=Ph (50%)
9 R= Ph (44%)
10 R= CH_3 (70%)

Chart I



for example, **11**, with the previously studied dienes **13**[2b] and **14**.[2c] In our diene the presence of the alkoxy substituent cis to the allylic carbon was anticipated to disfavor the "inside alkoxy isomer" **11b**, thereby yielding complete π-face selectivity via conformer **11a**.[17,18] In the event diene

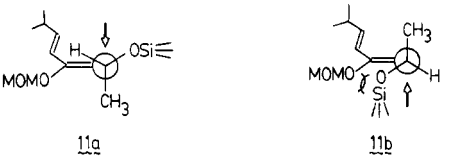


10 R=H
11 R=Si

13

14

(reacts via conformer **1a**) (reacts via conformer **1b**)



11a **11b**

11 reacted smoothly with *N*-phenylmaleimide to produce the Diels–Alder adduct **15** as the exclusive diastereomer.[19,20] This is the first diene containing an allylic chiral

(7) Murai, A.; Abiko, A.; Shimada, N.; Masamune, T. *Tetrahedron Lett.* **1985**, *25*, 4951.

(8) Similar selectivity has been observed in both Pd-catalyzed alkylations and in the Claisen rearrangement, see: (a) Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448. (b) Parker, K. A.; Farmer, J. G. *Tetrahedron Lett.* **1985**, *26*, 3655.

(9) The enol ether is ready available from 2-chloroethanol as previously described for the THP derivative, see: Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.

(10) For additions of alkyllithiums to related enol and dienyl ethers, see: Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, *102*, 1577.

(11) For the phenyl diene **3** the addition reaction cannot be suppressed entirely, which accounts for the poor yield of **7**.

(12) The yields of **8–10** are all greater than 80% based on recovered starting diene. The recovery of starting material does not seem to be a function of incomplete deprotonation or of protonation by the aldehyde (note the higher yield of **10** vs. **8**). The exact origin of this problem is not known at present.

(13) New compounds have been fully characterized by spectral means and elemental composition.

(14) Such enol aldol products have been prepared previously from β-lithiated enol ethers, which themselves were obtained via metal/halogen (ref 15a) or metal/Sn (ref 15b,c) exchange. Further study of these compounds has been hampered by their propensity to hydrolyze to α,β-unsaturated ketones. We have been pleasantly surprised by the stability of our compounds (**7–10**) toward hydrolysis; more specifically, we have never seen any decomposition during silica gel chromatography (For a similar observation see ref 15c).

(15) (a) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595. (b) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365. (c) McGarvey, G. J.; Bajwa, J. S. *J. Org. Chem.* **1984**, *49*, 4901.

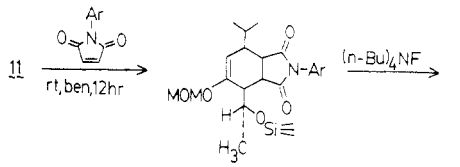
(16) Note in the ORTEP drawing (ref 19) the cis relationship of the isopropyl and the hydroxyethyl groups. This could only occur from the *Z* isomer **11**.

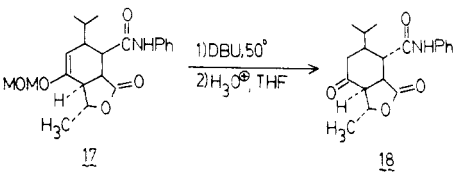
(17) It is well documented that cis substitution in asymmetric allylic alcohols often leads to high asymmetric induction. For numerous leading references, see ref 4c.

(18) While the effect of a substituent located cis to the chiral center has not previously been evaluated in the intermolecular Diels–Alder reaction, the π-face selectivity of an intramolecular Diels–Alder reaction is nicely controlled by such substituents (see ref 3). However, due to the additional conformational constraints of the intramolecular process the sense of the asymmetric inductions for the inter- vs. intramolecular reactions are reversed.

(19) The 300-MHz ^{1}H NMR spectrum of the crude reaction mixture shows no other diastereomer present. As minor isomers were produced (selectivity approximately 5:1) when the free alcohol **10** was used as diene, we are sure that ^{1}H NMR spectrum can distinguish the diastereomers.

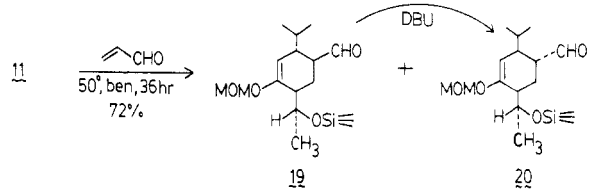
center which exhibits complete face selectivity in the intermolecular Diels–Alder reaction. While this product could be cleanly manipulated in a predictable fashion (**15** → **17** → **18**) none of these compounds revealed the relative stereochemistry between the preexisting exocyclic chiral center and the newly created ring chiral centers. For this





assignment we relied on an X-ray crystal structure of the bromo derivative **16**[21] derived from the Diels–Alder reaction of diene **11** with *N*-*p*-bromophenylmaleimide. This structure confirms that diene **11** and **13** exhibit the same facial selectivity in keeping with Franck's recently proposed selection rule.[2b] As just hypothesized the increased selectivity can be directly attributed to the presence of the *Z*-alkoxy substituent, which forces the reaction to proceed from conformer **11a** via the expected endo transition state. An additional, and perhaps undervalued, effect of the alkoxy substituent is to cant the transition state toward the carbon bearing the largest orbital coefficient.[22] In the case of alkoxy diene **11** this would maximize the effect of the chiral allylic carbon (see Chart I). It should be noted that the alkoxy substituent in diene **14** would distort the transition state away from the asymmetric centers which might be at least partially responsible for the decreased selectivity observed in that system.[2c,23]

Finally, in a more traditional vein, the alkoxy substituent can control the regiochemistry of the Diels–Alder reaction as evidenced by the addition of acrolein. The major product **19** was accompanied in this instance by a small amount of a minor isomer **20** (ratio 13:1). The identity



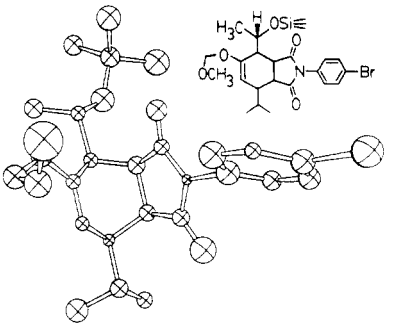
of this minor isomer was easily established by a base-catalyzed interconversion of **19** to **20**,[24] which confirmed that the face selectivity exhibited by diene **11** was again complete.

In conclusion the placement of an electron-donating substituent, such as an alkoxy group, cis to the chiral allylic carbon of a diene is unique in its ability to control both the stereoselectivity and regiochemistry of the intermolecular Diels–Alder reaction. Such systems are easily accessed by the direct β-lithiation of an alkoxy diene. The combination of these two methodologies accounts for the stereocontrolled introduction of five-contiguous asymmetric centers in two steps. Plans to utilize this strategy in natural product synthesis are currently under way in our laboratories.

Acknowledgment. This research was supported by a grant from Research Corporation. Acknowledgement is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(20) **15**: mp 117–119 °C (acetone/H_2O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24–7.06 (3 H, m), 6.96 (1 H, dd, *J* = 7.0, 1.5 Hz), 4.75 (1 H, A of an AB, *J* = 6.3 Hz), 4.64 (1 H, dd, *J* = 4.5, 2.0 Hz), 4.62 (1 H, B of an AB, *J* = 6.3 Hz), 4.59 (1 H, dq, *J* = 10.2, 5.8 Hz), 3.54 (1 H, dd, *J* = 8.5, 4.5 Hz), 3.17 (1 H, dd, *J* = 8.5, 6.0 Hz), 3.07 (3 H, s), 2.23 (1 H, ddd, *J* = 10.2, 4.5, 2.0 Hz), 1.92 (1 H, dp, *J* = 10.2, 6.4 Hz), 1.66 (1 H, ddd, *J* = 10.2, 6.0, 4.5 Hz), 1.17 (3 H, d, *J* = 5.8 Hz), 1.01 (3 H, d, *J* = 6.4 Hz), 0.82 (3 H, d, *J* = 6.4 Hz).

(21) The ^1H NMR spectrum for **16** was identical with that for **15** except for the aromatic region. Crystals of **16** (mp 122–124 °C) suitable for X-ray analysis were obtained from acetone/water. The ORTEP drawing, minus hydrogens, is shown.



(22) For a discussion of the asymmetry of the transition state for the Diels–Alder reaction, see: Dewar, M. J. S.; Pierini, A. B. *J. Am. Chem. Soc.* **1984**, *106*, 203.

(23) The reversal of face selectivity for **14** relative to other asymmetric dienes is more difficult to rationalize.

(24) The epimerization of both **17** and **19** yields exclusively one isomer (**18** and **20**). This allows selective entry to either of two diasteromeric series.

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Bengamides, Heterocyclic Anthelminthics from a Jaspidae Marine Sponge

Summary: The methanol extract of an undescribed Fiji sponge contains the novel seven-membered ring heterocycles, bengamide A (**1a**) and bengamide B (**2a**), which are cyclized by a δ-hydroxylysine. These compounds are biotoxic to eucaryotic cells, nematodes, and bacteria.

Sir: During two past expeditions to the Fiji Islands we collected an abundant, finger-like, orange sponge, which is an undescribed member of the Jaspidae family (order Choristida = Astrophorida).[1] Chemical studies were in-

(1) An underwater photograph of this sponge is available from P.C., and a voucher specimen has been deposited in the UCSC IMS collection. Taxonomic examination of our voucher specimens revealed the following properties. The dermal membrane contains numerous asters; strongyles are irregularly distributed and tangential to the surface. The choanosome contains numerous asters. Strongyles occur in loose bunches; some of them are connected by spongin. The asters measure 15 to 30 μm in diameter. The strongyles, which are often curved are a variety of sizes, from 520 × 5 to 680 × 8 to 600 × 17 μm. The sponge is an undescribed genus in the Jaspidae. It may belong to the subfamily Jaspinae, but it has strongyles whereas all genera previously described in this subfamily have only oxeas as macroscleres.

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