Carbohydrate-Derived Chiral Furanosidic α,β-Unsaturated Aldehydes in Conjugate and Diels–Alder Addition Reactions. Steric Hindrance by the Anomeric Substituent

Nicola Rehnberg, Anders Sundin, and Göran Magnusson*

Organic Chemistry 2, Chemical Center, Lund Institute of Technology, University of Lund, Box 124, S-221 00 Lund, Sweden

Received February 23, 1990

The title aldehydes (**1r**, **1s**, **2**, and **3**) underwent virtually diastereospecific conjugate addition by lithium methylcyanocuprate. The bulkiness of the anomeric benzyloxy or methoxy groups direct the attacking nucleophile to the less hindered side of the furanosidic ring. The stereochemical outcome of the Diels–Alder additions of cyclopentadiene to **1r** and **1s** was governed almost completely by the bulkiness of the anomeric benzyloxy group, which directed cyclopentadiene to the less hindered side of the furanosidic ring. When an additional substituent was positioned trans to the anomeric substituent (**2**), a mixture of all four possible diastereomers was obtained. With both substituents on the same side of the ring (**3**), complete π-facial selectivity was obtained. In both the conjugate and Diels–Alder addition products, NMR data could be used to determine the stereostructures of all diastereomers. Both product types showed oxygen atom induced proton deshielding and carbon shielding effects in NMR.

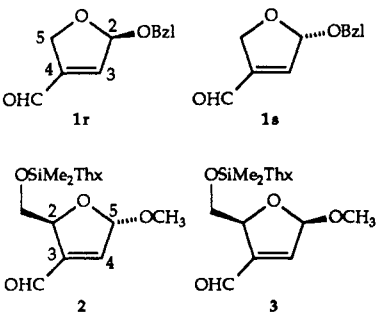
In the preceding paper[1] we reported on the synthesis of the chiral isoprenoid aldehydes[2] **1r** and **1s** as well as the preparation of the new chiral aldehydes **2** and **3** (Chart I) in 36 and 8% yields, respectively, over three steps starting from methyl α- and β-D-glucopyranoside. Hydrogenation of **1–3** gave the corresponding saturated aldehydes. Compounds **1r** and **1s** were used as starting materials in our syntheses of enantiomerically pure norbornenes,[3] botryodiplodin,[4] and lignans.[5] The key reactions in these syntheses were based on Diels–Alder reactions with cyclopentadiene[6] and virtually diastereo*specific* conjugate additions of lithium methylcyanocuprate (LiMeCuCN) and benzylic dithioacetal anions, respectively to aldehydes **1r** and **1s**.

Synthesis of enantiomerically pure tetrahydrofuran derivatives is currently being investigated by several research groups. Conjugate and Diels–Alder additions to chiral butenolides has furnished optically pure compounds of general utility.[7]

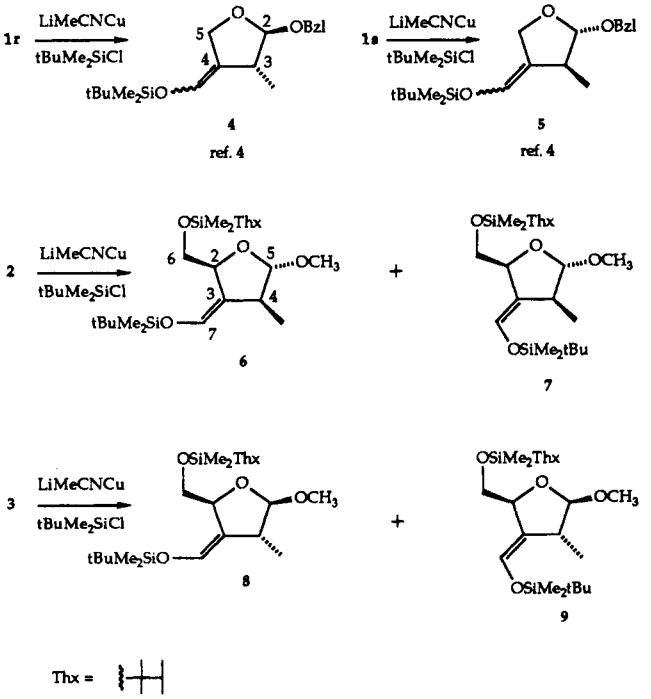
We now report investigations of conjugate and Diels–Alder addition reactions with the new aldehydes **2** and **3**.

Conjugate Additions. Conjugate addition of LiMeCuCN to the aldehydes **1r** and **1s** proceeded with high diastereoselectivity, thus furnishing the methyl derivatives **4** and **5** (Scheme I) by addition from the less hindered side of **1**. According to ^{1}H NMR, the crude product contained a small amount (approximately 3%) of a compound with a doublet a 5.00 ppm (J = 5.6 Hz).[4] However, chromatography of the crude mixture removed the isomer and gave pure **4** and **5** (de >99.4%). It seems improbable that the closely related cis isomer would have been removed so readily in this chromatographic process and, therefore,

Chart I



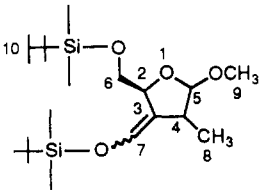
Scheme I



(1) Rehnberg, N.; Magnusson, G. *J. Org. Chem.*, preceding paper in this issue.
(2) Sundin, A.; Frejd, T.; Magnusson, G. *J. Org. Chem.* **1986**, *51*, 3927.
(3) Sundin, A.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1985**, *26*, 5605.
(4) (a) Rehnberg, N.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 3589. (b) Rehnberg, N.; Magnusson, G. *Acta Chem. Scand.* **1990**, *44*, 377.
(5) (a) Rehnberg, N.; Magnusson, G. *Tetrahedron Lett.* **1988**, *29*, 3599. (b) Rehnberg, N.; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 4340.
(6) Improved synthetic procedure: Magnusson, G. *J. Org. Chem.* **1985**, *50*, 1998.
(7) (a) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055. (b) Feringa, B. L.; de Jong, J. C. *J. Org. Chem.* **1988**, *53*, 1125.

0022-3263/90/1955-5477$02.50/0 © 1990 American Chemical Society

Table I. ^{1}H NMR Chemical Shifts (δ), Coupling Constants[a] (hertz), and NOE Data[b] (percent) for the Michael Adducts 6–9



cmpd		proton no. H-2	H-4	H-5	H-6a	H-6b	H-7	H-8	H-9	H-10	Me_2CH, MeC	MeSi
6	δ	4.75	2.58	4.69	4.04	3.69	6.23	1.06	3.35	1.65	0.91–0.86	0.12
	J	dt 7.0, 2.0	q[c] 7.2	s	dd 11.0, 2.1	dd 11.0, 7.0	dd 2.4, 1.2	d 7.2	s	h 6.8	m	s
	NOE	10 (H-6a)	6 (H-7)			31 (H-6a)						
7	δ	4.51	2.95	4.66	3.73	3.50	6.34	1.10	3.34	1.64	0.92–0.86	0.12, 0.11
	J	t 5.9	q[c] 7.2	s	dd 10.2, 5.5	dd 10.2, 6.0	t 1.8	d 7.2	s	h 6.8	m	s
	NOE	5 (H-7)										
8	δ	4.83	2.62	4.64	4.02	3.52	6.17	1.08	3.40	1.64	0.91–0.86	0.13, 0.12, 0.10
	J	dq 8.7, 2.1	qq 7.1, 1.6	d 1.7	ddd 10.6, 2.4, 0.5	dd 10.6, 8.8	dd 2.3, 1.6	d 7.2	s	h 6.8	m	s
	NOE		5 (H-7)	5 (H-4)			3 (H-4)					
9	δ	4.58	3.00	4.62	3.68	3.45	6.39	1.12	3.31	1.64	0.92–0.86	0.11, 0.10
	J	dd 7.1, 5.9, 2.0	tq 7.3, 1.7	s	dd 9.6, 6.0	dd 9.6, 7.0	t 1.6	d 7.2	s	h 6.9	m	s
	NOE	6 (H-7)			3 (H-7)							

[a] s = singlet, d = doublet, t = triplet, q = quartet, h = heptet. [b] The NOE is given in percent, followed by the irradiated proton in parentheses. [c] Additional small coupling(s) was observed.

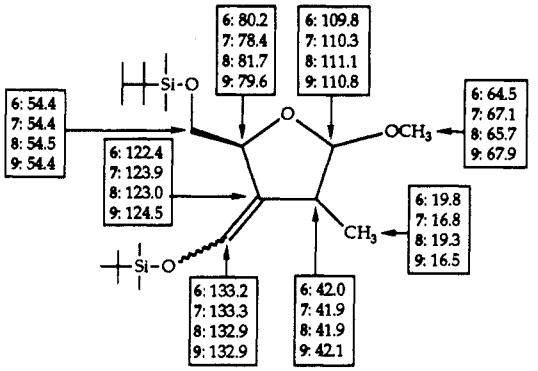


Figure 1. ^{13}C NMR chemical shifts (δ relative to Me_4Si) for compounds 6–9.

we beleive that the doublet at 5.00 ppm emanates from some other (unidentified) compound. Furthermore, conjugate addition of dithioacetal anions to **1** proceeded with virtually complete diastereoselectivity.[5] Therefore, it is probable that the conjugate addition in reality proceeded with a very high diastereomeric excess, similar to the reactions with **2** and **3** (see below).

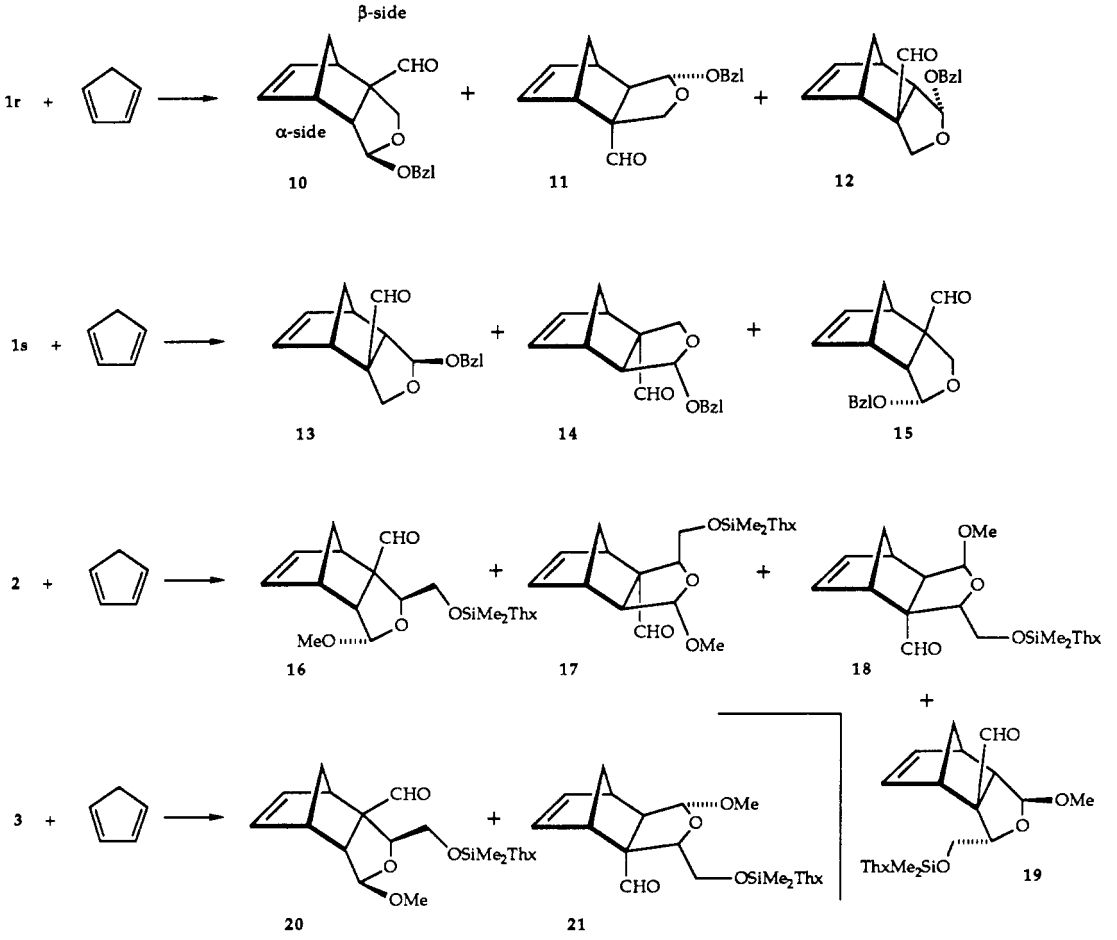
In the conjugate addition of LiMeCuCN to **1**, *tert*-butyldimethylsilyl chloride ($tBuMe_2SiCl$) was used for trapping of the intermediate enolate, which resulted in 87% yield of the corresponding silyl enol ether.[4] In the absence of $tBuMe_2SiCl$, the corresponding aldehyde was formed but the yield was only 12%. Therefore, the experiments with **2** and **3** were performed in the presence of $tBuMe_2SiCl$.

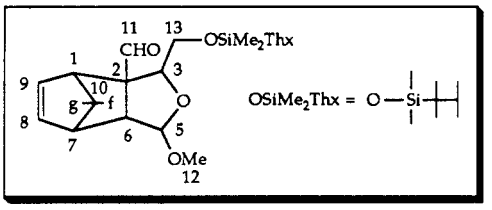
The 2,5-trans (for numbering, see Chart I) substituted aldehyde **2** carries a (silyloxy)methyl group that might hinder the approaching nucleophile and thereby lower the diastereoselectivity of the reaction. However, only the E/Z pair (ratio 7.5:1) **6** and **7** was formed in 61% yield and the possible 4,5-cis isomer could not be detected. As expected, the 2,5-cis substituted aldehyde **3** also reacted with complete diastereoselectivity and the E/Z pair (ratio 4.5:1) **8** and **9** was obtained in 77% yield. The very high diastereoselectivity of these reactions clearly shows that in furanosidic (and probably cyclopentenoid) systems, a γ-alkoxy substituent in an α,β-unsaturated aldehyde effectively directs the nucleophile to the less-hindered side of the ring. These results are important for the further utilization of **2** and **3** as chiral synthons.

The structure determination of **6–9** was based on NMR spectroscopic evidence (Table I and Figure 1). In all cases the H-5 (anomeric) signal was a singlet or a weakly coupled ($J < 2$ Hz) doublet, showing that H-4 and H-5 are trans situated.[8] The ^{13}C NMR spectra (Figure 1) were similar for **6–9**, indicating that they are stereoisomers. The E and Z configurations were determined by NOE measurements. Irradiation of the vinyl proton (H-7) gave a signal enhancement of approximately 5% on H-4 in **6** and **8** and on H-2 in **7** and **9**. Furthermore, a signal enhancement of 3% was obtained for one of the (silyloxy)methyl group protons (H-6) of **9**. In addition, the H-2 signals of **6** and **8** and the H-4 signals of **7** and **9** were deshielded by the neighboring oxygen atom by approximately 0.25 and 0.4 ppm, respectively (H-2–O-7 distance: **6**, 3.15 Å; **8**, 3.09 Å, H-4–O-7 distance: **7**, 2.90 Å; **9**, 3.22 Å; calculated by energy minimization using the MM2 program[9]). Such deshielding was also observed with some of the norbornanes below and with various oligosaccharides.[10] With the latter, the deshielding was used to corroborate the conformational analysis of a series of disaccharide analogues. As postulated,[10] the deshielding effect requires that the proton and

(8) Stevens, J. D.; Fletcher, H. G., Jr. *J. Org. Chem.* **1968**, *33*, 1799.
(9) Molecular construction and MM2 calculations were performed on a Macintosh II computer, using our molecular modeling program MACMIMIC and a Macintosh II version of the MM2 program. The latter has been described: Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982. The MM2 program is available for main-frame computers through QCPE, Department of Chemistry, Indiana University, Bloomington, IN 47405, for academic users, and through Molecular Design Ltd., 2132 Farallon Drive, San Leandro, CA 94577, for nonacademic users.
(10) (a) Thögersen, H.; Lemieux, R. U.; Bock, K.; Meyer, B. *Can. J. Chem.* **1982**, *60*, 44. (b) Bock, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Carbohydr. Res.* **1988**, *176*, 253.

Scheme II

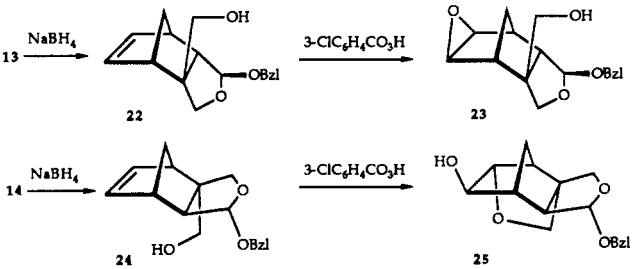




the oxygen atom are in repulsive van der Waals contact (i.e., <2.7 Å) with each other. However, according to the energy-minimized conformations of **6–9**, the hydrogen–oxygen distances were somewhat longer (see above).

Diels–Alder Reactions. Treatment of **1r** and **1s** with cyclopentadiene[6] below room temperature gave the norbornene derivatives **10/11** and **13/14**, respectively (Scheme II) via addition to the less hindered side of the aldehydes. At 50 °C, or with tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione)europium(III) [Eu(fod)$_3$] catalysis, a small amount (<5%) of **12** and **15** was also obtained via addition to the more hindered side of **1r** and **1s**. In the 2,5-trans-substituted aldehyde **2**, both sides of the furanosidic ring are hindered by the methoxy or (silyloxy)methyl group and all four possible diastereomers (**16–19**) were formed. The 2,5-cis substituents of aldehyde **3** seem to direct the addition completely to the less hindered side of the furanosidic ring and the norbornenes **20** and **21** were the only products formed, even with Eu(fod)$_3$ catalysis. The bulky (silyloxy)methyl group of **2** is more hindering than the methoxy group in Diels–Alder additions as revealed by the (**16** + **18**):(**17** + **19**) ratio of approximately 3.3. Exo addition is favored over endo addition with all the aldehydes **1–3**. This is in contrast to the outcome of most Diels–Alder additions with α,β-unsaturated dienophiles,[11] although other such exceptions are known.[12] In exo addition to **2**, the (silyloxy)methyl group excerts the greatest steric hindrance, which is reflected by the **16/19** ratio (18:1). In endo addition, the two groups excert similar hindrance as shown by the **17/18** ratio (approximately 1:1). In the presumed transition state of exo addition, two sp^2

Scheme III



(11) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: London, New York, 1981; p 841.
(12) (a) Thomas, A. F.; Willhalm, B. *Helv. Chim. Acta* **1967**, *50*, 826. (b) Lindsay Smith, J. R.; Norman, R. O. C.; Stillings, M. R. *Tetrahedron* **1978**, *34*, 1381.

carbons of cyclopentadiene are required to reside over the furanosidic ring, whereas in endo addition, only one sp^3 carbon occupies such a position.

Structure determination of the norbornene derivatives **10–21** was based on chemical transformations (Scheme III) and NMR spectroscopic evidence in comparison with literature data.[13] The alcohols **22** and **24** obtained by sodium borohydride reduction of **13** and **14**, on treatment with *m*-chloroperbenzoic acid, gave the epoxide **23** and the cyclic ether **25**, clearly showing that the formyl groups of **13** and **14** were placed in the exo and endo position, respectively (Scheme III). NMR data for **23** and **25** were substantially similar to literature data of other norbornane epoxides and cyclic ethers.[13c,d] The ^1H NMR spectrum of **23** showed a pair of doublets (J = 3.0 Hz) at 3.37 and 3.19 ppm and the ^{13}C NMR spectrum showed signals at 49.8 and 49.3 ppm, typical for epoxides. The H-10f proton (Table II) is shielded by the epoxide ring[13c] and appears as a doublet (J = 8.4 Hz) at 1.00 ppm. The HO signal was a triplet as expected for a primary alcohol. The cyclic ether **25** showed a singlet for H-9, which means that it is situated trans to H-8. Both H-10 protons are deshielded almost to the same extent, indicating that they both are in close contact with an oxygen atom (see above). The distance between H-10g and the hydroxyl group and between H-10f and the ring oxygen atom was calculated[9] to be 2.63 Å and 2.62 Å, respectively. The HO signal was a doublet as required for a secondary alcohol. The structural proof for **23** and **25** clearly defines the exo and endo position of the formyl groups (and thereby the corresponding endo and exo configuration of the tetrahydrofuran ring) in **13** and **14**, respectively.

With the structures of **13** and **14** in hand, detailed analysis of the NMR data for **10–25** allowed the formulation of general rules for the structural analysis of these compounds: (i) compounds having the furanosidic ring in the endo position (as in **10**) have similar chemical shifts for the H-10 protons (1.3–1.7 ppm); (ii) when the furanosidic ring is in the exo position (as in **11**), H-10f is deshielded and appears at 1.85–2.08 ppm; (iii) with the formyl group in the exo or endo position (as in **10** or **11**), the H-11 (formyl) proton appears at approximately 9.8 or 9.5 ppm, respectively; (iv) the ^{13}C NMR chemical shift for C-10 is approximately 51 or 44 ppm for the compounds with the furanosidic ring endo or exo, respectively; (v) for compounds with H-5 and H-6 trans situated, H-5 appears as a singlet; (vi) for compounds with H-5 and H-6 cis situated, H-5 appears as a doublet (approximately 6 Hz). In addition, the configuration at positions 3 and 5 in compounds **16–21** are mutually dependent. These rules can be used as the basis for determining the stereostructures of **10–21** and the NMR data (Table II and Figure 2) were found to be in perfect accord with the structures.

NOE measurements were performed with compounds **16–21** in order to corroborate the structural analyses. The experiments were performed with the pure compounds except for **16** and **17**, which we could only isolate as a mixture. The NOE enhancements are shown in Table II.

Irradiation of H-9 and H-11 in **16** enhanced the H-3 and H-13 signals, respectively, showing that the furanosidic ring is endo situated with the (silyloxy)methyl group cis to the formyl group. The H-5 signal is a singlet and therefore

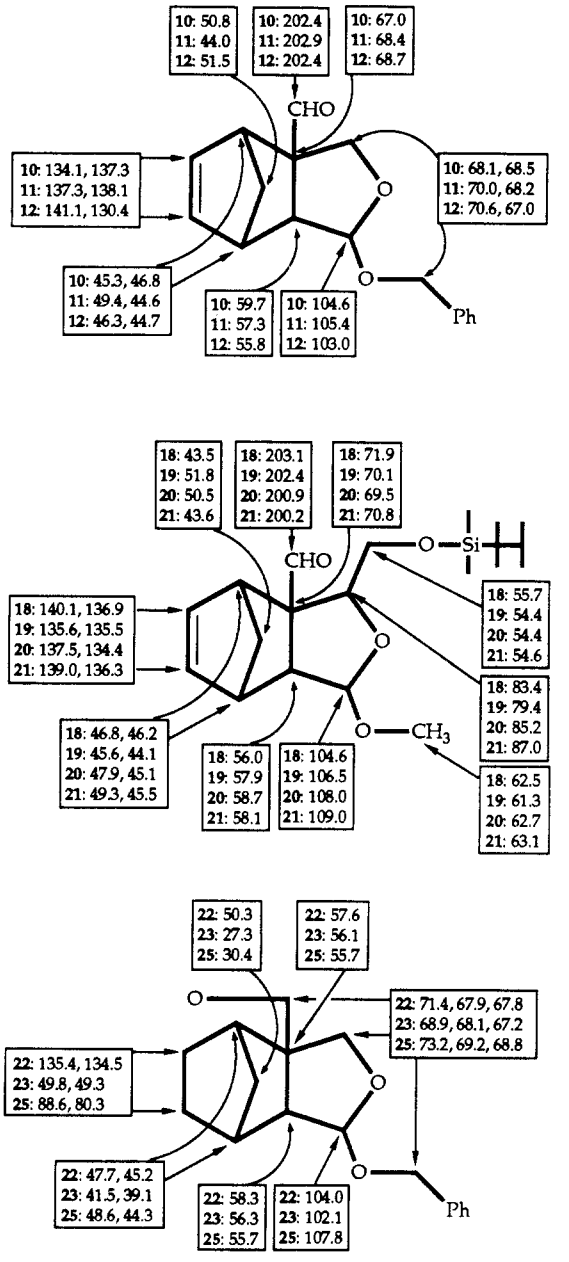
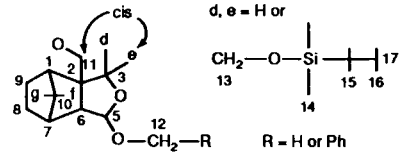


Figure 2. ^{13}C NMR chemical shifts (δ relative to Me_4Si) for compounds **10–12**, **18–23**, and **25**.

the methoxy group is situated on the α side of the ring system. Irradiation of H-5 in **17** enhanced the H-13, H-7, and H-10f signals, which shows that H-5 is situated on the β side of the ring system and confirms the exo configuration of the furanosidic ring. Further corroboration was obtained from irradiation of the formyl proton H-11, which enhanced the H-9 and H-3 (but not H-13) signals. Irradiation of H-10f in **18** gave a strong enhancement of the H-3 signal, which as a matter of fact settles the complete stereostructure. In addition, irradiation of H-11 gave a weak enhancement of the H-9 signal. Irradiation of H-5 in **19** enhanced the H-8 signal, which shows that the furanosidic ring is endo situated and that the methoxy group is on the β side of the ring system. Furthermore, irradiation of H-11 gave a strong enhancement of the H-3 signal, showing that the (silyloxy)methyl group is situated on the α side of the ring system. Irradiation of H-5 and H-8,9 in **20** enhanced the H-8 and H-3,5 signals, respectively. In addition, irradiation of H-11 enhanced the H-12 and H-13 signals. This shows that the furanosidic ring is endo situated and that all the substituents are positioned on the

(13) (a) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107. (b) Werstiuk, N. H.; Taillefer, R.; Bell, R. A.; Sayer, B. *Can. J. Chem.* **1973**, *51*, 3010. (c) Zimmermann, D.; Reisse, J.; Coste, J.; Plénat, F.; Christol, H. *Org. Magn. Reson.* **1974**, *6*, 492. (d) Kleinpeter, E.; Kühn, H.; Mühlstädt, M. *Org. Magn. Reson.* **1977**, *9*, 90. (e) Ward, D. D.; Shafizadeh, F. *Carbohydr. Res.* **1981**, *95*, 155.

Table II. ^{1}H NMR Chemical Shifts (δ), Coupling Constants[a] (hertz), and NOE Data[b] (percent) for Compounds 10–25



cmpd		proton no. H-1	H-3d	H-3e	H-5	H-6	H-7	H-8	H-9	H-10f	H-10g	H-11	H-12	H-13	H-13′	H-14	H-15	H-16	H-17	OH
10	δ	3.17	3.53	4.10	4.81	3.00	3.08	6.26[c]	6.25[c]	1.55	1.55	9.84	4.66, 4.42							
	J	m	d 9.7	d 9.7	s	d 4.1	m	dd 4.5, 2.9	dd 4.5, 2.9	s	s	s	AB q 12.1							
11	δ	2.93	3.72	4.37	5.00	2.43	2.93	6.31[c]	6.26[c]	1.99	1.41	9.51	4.70, 4.46							
	J	br s	d 9.6	d 9.6	s	d 1.6	br s	dd 5.3, 3.0	dd 5.3, 3.0	d 9.1	dd 9.1, 1.5	s	AB q 12.0							
12	δ	3.0	3.53	3.96	5.10	3.16	3.05	6.49	6.12	1.66[c]	1.69[c]	9.80	4.76, 4.45							
	J	m	d 9.5	d 9.5	d 5.9	dd 5.9, 3.7	m	dd 5.6, 2.9	dd 5.6, 3.4	td 8.8, 1.6	td 8.8, 1.6	s	AB q 12.0							
16	δ	3.08	3.75		5.08	1.57–1.35	2.94	6.44	6.12	1.57–1.35	1.57–1.35	9.86	3.36	3.61	3.34	0.08	0.84	0.88	1.61	
	J	s	dd 6.5, 3.7		d 6.1	m	s	dd 5.5, 3.1	dd 5.5, 3.1	m	m	s	s	dd 11.4, 6.7	dd 9.9, 3.8	s	s	d 6.9	h 6.9	
	NOE	7 (H-9) 6 (H-11)	7 (H-9) 4(H-11)					3 (H-9)						4 (H-11)						
17	δ	3.11		4.35	4.70	2.45	2.90	6.26	6.32	1.94	1.61–1.36	9.47	3.33	3.86	3.72	0.14, 0.12	0.84	0.86	1.61–1.36	
	J	s		dd 7.5, 6.1	s	s	s	dd 5.5, 3.1	dd 5.6, 2.8	d 9.3	m	s	s	dd 10.2, 6.0	dd 10.7, 7.3	s	s	d 7.2	m	
	NOE			6 (H-11)		4 (H-11, 5)	4 (H-5)		2 (H-11)	3 (H-5)				4 (H-5)						
18	δ	3.05	3.99		5.07	2.75	2.94	6.18[c]	6.21[c]	2.08	1.56	9.60	3.40	3.77	3.57	0.10, 0.09	0.84	0.88	1.62	
	J	s	dd 6.9, 4.4		d 6.4	dd 6.3, 1.7	s	dd 5.6, 2.7	dd 5.6, 3.1	d 9.0	dd 9.2, 1.8	s	s	dd 10.5, 4.4	dd 10.5, 6.8	s	s	d 6.8	h 6.9	
	NOE	2 (H-11)	15 (H-10f)			4 (H-11)			3 (H-11)		24 (H-10f)									
19	δ	3.22		4.31	4.46	2.94	3.01	6.18	6.25	1.54[c]	1.44[c]	9.73	3.29	3.79	3.54	0.12, 0.10	0.83	0.87	1.57	
	J	s		dd 8.1, 5.9	s	d 4.7	s	dd 5.2, 2.6	dd 5.3, 3.1	d 9.3	d 8.9	s	s	dd 10.0, 5.9	dd 10.0, 8.3	s	s	d 7.3	h 6.9	
	NOE	2 (H-11)		9 (H-11)		4 (H-11, 5)		5 (H-5)					6 (H-5)							
20	δ	3.07	3.78		4.52	1.26[c]	3.03	6.30	6.30	1.30[c]	1.50[c]	9.84	3.25	3.72	3.58	0.08, 0.07	0.82	0.86	1.60	
	J	d 4.4	dd 9.9, 3.9		s	m	s	s	s	dt 8.8, 1.4	dd 8.8, 1.6	s	s	t 9.2	dd 8.6, 3.8	s	s	d 6.9	h 5.7	
	NOE	5 (H-11) 3 (H-9)	3 (H-9)		2 (H-8)		6 (H-5) 3 (H-8)	5 (H-5)					5 (H-11) 7 (H-5) 3 (H-8,9)		5 (H-11)					
21	δ	3.04	4.05		4.72	2.58	2.86	6.20	6.20	1.92	1.43	9.58	3.30	3.69	3.62	0.09, 0.06	0.83	0.87	1.60	
	J	d 1.3	dd 9.5, 5.3		s	t 0.8	s	s	s	dd 9.0, 1.5	dd 9.0, 1.7	s	s	t 9.7	dd 9.9, 5.3	s	s	d 6.9	h 6.8	
	NOE	3 (H-11,9)			3 (H-6)	5 (H-11) 2 (H-8) 4 (H-5)	3 (H-8) 7 (H-5)	4 (H-6)	5 (H-11)	2 (H-5) 2 (H-6)		2 (H-8,9) 5 (H-6)	6 (H-5)	3 (H-11)						
22	δ	2.70	3.50	3.88	4.75	2.52	2.97	6.24[c]	6.16[c]	1.55[c]	1.52[c]	3.71	4.65, 4.40							2.33
	J	bs	d 9.2	d 9.4	s	d 3.9	bs	dd 5.5, 3.1	dd 5.5, 3.1	d 8.5	d 8.5	d 4.8	AB q 12.0							t 5.1
23	δ	2.49	4.03	3.87	5.08	2.29	2.68	3.37[c]	3.19[c]	1.00	1.50	3.64, 3.61	4.67, 4.47							2.01
	J	s	d 8.1	d 8.1	s	d 3.6	bs	d 3.0	d 3.0	d 8.4	d 8.4	d AB q, 8.7, 4.5, 3.0	AB q 9.9							t 3.9
24	δ	2.67	3.74	4.19	4.94	1.77	2.79	6.18	6.18	1.94	1.35	3.51, 3.47	4.70, 4.45							2.13
	J	bs	d 9.1	d 9.0	s	s	bs	m	m	d 8.9	d 8.9	d AB q 10.0, 6.7, 3.5	AB q 12.0							dd 6.5, 3.7
25	δ	2.23[c]	3.74	3.86	4.94	1.77[c]	1.95[c]	3.55[c]	3.97[c]	1.85[c]	1.82[c]	3.98, 3.91	4.70, 4.46							2.42
	J	s	d 8.0	d 8.0	s	bs	s	bs	s	d 9.6	d 9.6	AB q 9.5	AB q 9.9							d 4.2

[a] s = singlet, d = doublet, t = triplet, q = quartet, h = heptet. [b] The NOE is given in percent, followed by the irradiated proton in parentheses. [c] Assignment may be reversed.

β side of the ring system. Irradiation of H-5 in **21** gave a weak enhancement of the H-10f signal. Irradiation of H-6 and H-8 gave weak enhancements of the H-8 and H-6,11 signals, respectively. Finally, irradiation of H-11 gave enhancements of the H-8 and H-13 signals. These experiments clearly show that the furanosidic ring is exo situated in **21** and that all substituents are positioned on the α side of the ring system.

Conclusions. The stereochemical outcome of conjugate additions to the aldehydes **1–3** is governed by the bulkiness of the anomeric benzyloxy and methoxy groups, which direct the attacking nucleophile to the less hindered side of the furanosidic ring. The addition proceded with virtually complete diastereospecificity. The coupling constant of the anomeric (H-2 or H-5; Chart I) proton is a reliable diagnostic of the stereostructure (trans protons <2 Hz; cis protons[4] approximately 4.6 Hz).

The Diels–Alder additions to **1r** and **1s** were governed almost completely by the bulkiness of the anomeric benzyloxy group of the aldehyde, thus directing cyclopentadiene to the less hindered side of the furanosidic ring. When an additional substituent was positioned trans to the anomeric substituent, a mixture of all four possible diastereomers was obtained. With both substituents on the same side of the ring (as in **3**) complete π-facial selectivity was obtained.

In both the conjugate and the Diels–Alder addition products, ^{1}H and ^{13}C NMR data could be used to determine the complete stereostructures of all diastereomers. Both product types showed examples of proton deshielding and carbon shielding effects in NMR, emanating from close contacts between hydrogen and ether or alcohol oxygen atoms.

Experimental Section

Liquid chromatography purifications were performed in the gravity mode. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Melting points are uncorrected. NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are given in ppm downfield from Me_4Si with reference to internal $CHCl_3$ (7.26 ppm). The heptane used is a mixture of isomers with a boiling range of 94–100 °C. The syntheses of the following compounds have been described: **1r**[2], **1s**[2], **4**[4] and **5**.[4]

(+)-(2*S*,4*S*,5*S*)-2-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-3-[[(*Z*)-(*tert*-butyldimethylsilyl)oxy]methylene]-5-methoxy-4-methyltetrahydrofuran (6) and (+)-(2*S*,4*S*,5*S*)-2-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-3-[[(*E*)-(*tert*-butyldimethylsilyl)oxy]methylene]-5-methoxy-4-methyltetrahydrofuran (7). Methyl lithium in diethyl ether (0.54 mL, 1.6 M) was added to an ice-cooled slurry of cuprous cyanide (77.6 mg, 0.87 mmol) in tetrahydrofuran (2.7 mL). After 5 min the mixture was cooled with a dry ice/acetone bath and a solution of *tert*-butyldimethylsilyl chloride (131 mg, 0.87 mmol) in tetrahydrofuran (0.64 mL) was added. Compound **2** (200 mg, 0.67 mmol) was dissolved in tetrahydrofuran (2.0 mL) and added dropwise to the cooled lithium methylcyanocuprate mixture. After 5 min the mixture was allowed to reach room temperature and diethyl ether (10 mL) and aqueous ammonium sulfate (10%, 5 mL) were added. The aqueous phase was extracted with diethyl ether (5 mL) and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (5 mL) and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed (SiO_2, heptane/EtOAc 30:1) to give (in order of elution) **7** [24 mg, 8%; $[\alpha]^{25}_D$ +64.5° (*c* 1.3, $CHCl_3$)] and **6** [151 mg, 53%; $[\alpha]^{25}_D$ +104.9° (*c* 0.9, $CHCl_3$)]. For ^{1}H and ^{13}C NMR data, see Table I and Figure 1, respectively. Anal. (**6**) Calcd for $C_{22}H_{46}O_4Si_2$: C, 61.3; H, 10.8. Found: C, 61.2; H, 10.9.

(+)-(2*S*,4*R*,5*R*)-2-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-3-[[(*Z*)-(*tert*-butyldimethylsilyl)oxy]methylene]-5-methoxy-4-methyltetrahydrofuran (8) and (-)-(2*S*,4*R*,5*R*)-2-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-3-[[(*E*)-(*tert*-butyldimethylsilyl)oxy]methylene]-5-methoxy-4-methyltetrahydrofuran (9). Compound **3** (200 mg, 0.67 mmol) was added as above to lithium methylcyanocuprate and worked up to give (in order of elution) **9** [41 mg, 14%; $[\alpha]^{25}_D$ −48.2° (*c* 0.7, $CHCl_3$)] and **8** [182 mg, 63%; $[\alpha]^{25}_D$ +13° (*c* 1.1, $CHCl_3$)]. For ^{1}H and ^{13}C NMR data, see Table I and Figure 1, respectively. Anal. (**8**) Calcd for $C_{22}H_{46}O_4Si_2$: C, 61.3; H, 10.8. Found: C, 61.2; H, 11.0.

(-)-(1*R*,2*R*,5*R*,6*R*,7*S*)-2-Formyl-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (10), (-)-(1*S*,2*R*,5*R*,6*R*,7*R*)-2-Formyl-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (11), and (-)-(1*S*,2*S*,5*R*,6*S*,7*R*)-2-Formyl-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (12). (a) The aldehyde **1r**[2] (1.1 g, 5.4 mmol) and cyclopentadiene[6] (1.1 g, 16 mmol) were dissolved in toluene (8 mL), and the mixture was heated at 50 °C in a closed ampule for 24 h. Toluene and residual cyclopentadiene were removed and the residue was chromatographed (SiO_2, heptane/EtOAc 10:1) to give **10** [912 mg, 63%; $[\alpha]^{23}_D$ −113° (*c* 0.6, $CDCl_3$)], **11** [266 mg, 18%; $[\alpha]^{23}_D$ −119° (*c*, 0.8, $CDCl_3$)], and **12** [23 mg, 2%; $[\alpha]^{23}_D$ −19° (*c* 1.8, $CDCl_3$)]. For ^{1}H and ^{13}C NMR data, see Table II and Figure 2, respectively.

(b) Aliquots of the reaction mixture [prepared as in (a) above] were kept at various temperatures and reaction times. The products were analyzed by GLC and the relative amounts of **10**, **11**, and **12** are reported in the table of ref 3.

(+)-(1*S*,2*S*,5*S*,6*S*,7*R*)-2-Formyl-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (13) and (+)-(1*R*,2*S*,5*S*,6*S*,7*S*)-2-Formyl-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (14). (a) The aldehyde **1s**[2] (3.2 g, 15.7 mmol) and cyclopentadiene[6] (3.5 g, 51 mmol) were dissolved in toluene (10 mL), and the mixture was stirred at room temperature for 36 h. Workup as above (a) gave **13** [2.72 g, 64%; $[\alpha]^{23}_D$ +114° (*c* 0.7, $CDCl_3$)], **14** [0.64 g, 15%; $[\alpha]^{23}_D$ +118° (*c* 0.4, $CDCl_3$)], and a **13**/**14** mixture (0.34 g, 8%). For ^{1}H and ^{13}C NMR data, see Table II and Figure 2, respectively. When the reaction was run at 50 °C (cf. the preparation of **10–12**), a small amount of **15** was also isolated.

(1*R*,2*R*,3*S*,5*S*,6*R*,7*S*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (16), (1*R*,2*S*,3*S*,5*S*,6*S*,7*S*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (17), (+)-(1*S*,2*R*,3*S*,5*S*,6*R*,7*R*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (18), and (+)-(1*S*,2*S*,3*S*,5*S*,6*S*,7*R*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (19). The aldehyde **2**[1] (200 mg, 0.66 mmol), cyclopentadiene[6] (220 mg, 3.34 mmol), and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione)europium(III) [Eu(fod)$_3$, 30 mg, 0.029 mmol] were dissolved in toluene (1 mL), and the mixture was left at room temperature for 24 h. Toluene and residual cyclopentadiene were removed and the residue was chromatographed (SiO_2, heptane/EtOAc 30:1) to give (in order of elution) **18** [43 mg, 15%; $[\alpha]^{25}_D$ +53.4° (*c* 2.1, $CHCl_3$)], **16** and **17** (143 mg, 50%; inseparable mixture 3:1), and **19** [15 mg, 5%; $[\alpha]^{25}_D$ +34.4° (*c* 1.5, $CHCl_3$)]. For ^{1}H and ^{13}C NMR data, see Table II and Figure 2, respectively. Anal. (**19**) Calcd for $C_{20}H_{34}O_4Si$: C, 65.5; H, 9.4. Found: C, 65.2; H, 9.3.

(-)-(1*R*,2*R*,3*S*,5*R*,6*R*,7*S*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (20) and (-)-(1*S*,2*R*,3*S*,5*R*,6*R*,7*R*)-3-[[[Dimethyl(1,1,2-trimethylpropyl)silyl]oxy]methyl]-2-formyl-5-methoxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (21). The aldehyde **3**[1] (100 mg, 0.33 mmol) was treated for 2.5 h as in the preparation of **16–19** to give (in order of elution) **21** [32 mg, 26%; $[\alpha]^{25}_D$ −71.5° (*c* 2.1, $CHCl_3$)] and **20** [41 mg, 34%; $[\alpha]^{25}_D$ −2.5° (*c* 2.7, $CHCl_3$)]. For ^{1}H and ^{13}C NMR data, see Table II and Figure 2, respectively.

(+)-(1*S*,2*S*,5*S*,6*S*,7*R*)-2-(Hydroxymethyl)-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (22). The aldehyde **13** (123 mg, 0.45 mmol) was dissolved in ethanol (8 mL) and sodium borohydride (7 mg, 0.185 mmol) was added. The mixture was sonicated for 30 s and then left at room temperature for 30 min. Acetone (3 drops) was added, and after 30 min, the solvent was removed and the residue was dissolved in dichloromethane and washed with water. The solvent was removed and the residue was filtered through silica (CH_2Cl_2) to give **22** [81 mg, 65%); $[\alpha]^{23}_D$

+110° (c 3.1, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Epoxide 23. Compound **22** (150 mg, 0.55 mmol) was dissolved in dichloromethane (5 mL) and cooled (ice bath). *m*-Chloroperbenzoic acid (150 mg, 0.65 mmol, 70%) was added and the mixture was left (ice bath) for 12 h and then chromatographed (Al_2O_3, CH_2Cl_2/EtOAc 1:1) to give **23** [oil, 68 mg, 43%; $[\alpha]^{23}_D$ +64° (c 1.35, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

(+)-(1*R*,2*S*,5*S*,6*S*,7*S*)-2-(Hydroxymethyl)-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (24). The aldehyde **14** (123 mg, 0.45 mmol) was treated as in the preparation of **22** to give **24** [120 mg, 93%; $[\alpha]^{23}_D$ +92.5° (c 1.9, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Alcohol 25. Compound **24** (100 mg, 0.37 mmol) was treated as in the preparation of **23** to give **25** [65 mg, 61%; mp 104–105 °C; $[\alpha]^{23}_D$ +96° (c 0.6, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Acknowledgment. We thank Maria Levin for technical assistance. This work was supported by The Swedish Natural Science Research Council and The Swedish National Board for Technical Development.

Registry No. **1r**, 104322-41-0; **1s**, 104322-42-1; **2**, 128843-75-4; **3**, 128945-87-9; **6**, 128846-17-3; **7**, 128846-18-4; **8**, 128869-12-5; **9**, 128846-19-5; **10**, 104816-20-8; **11**, 104873-09-8; **12**, 104873-10-1; **13**, 104873-11-2; **14**, 104873-12-3; **15**, 104873-13-4; **16**, 128846-20-8; **17**, 128945-99-3; **18**, 128946-00-9; **19**, 128946-01-0; **20**, 128946-02-1; **21**, 128846-21-9; **22**, 104816-21-9; **23**, 104816-22-0; **24**, 104873-14-5; **25**, 104816-23-1; cyclopentadiene, 542-92-7.

Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **10**, **11**, **15**, **18**, **20**, **21**, **22**, and **24** (15 pages). Ordering information is given on any current masthead page.

Total Synthesis of Indole Alkaloids. A New Strategy for (±)-19-Oxoaspidospermidine and (±)-19-Oxoaspidofractinine

M. Dufour,† J.-C. Gramain,*,† H.-P. Husson,‡ M.-E. Sinibaldi,† and Y. Troin†

Chimie des Substances Naturelles, U.R.A. 485, Université Blaise Pascal, 63177 Aubiere Cedex, France, and Faculté des Sciences Pharmaceutiques et Biologiques, U.R.A. 1310 du CNRS, 4, Avenue de l'Observatoire, 75270 Paris Cedex-06, France

Received March 13, 1990

A synthesis for the preparation of 19-oxoaspidospermidine (1) and 19-oxoaspidofractinine (2) has been developed beginning with tetracyclic amido alcohol **9**. Dehydration of **9** gave enamide **10**. Reduction to the corresponding enamine followed by reaction with acetyl chloride afforded the tetracyclic enamino ketone **12**. Studies on the selective reduction of the olefinic bond of the enamino ketone moiety of **12** were carried out. Removal of N-4 protecting group and further alkylation with a three carbon atoms appendage gave compounds **17**. Cyclization to pentacyclic product **18** was achieved using NaH in a benzene/THF solution. After deprotection of the N-1 atom and oxidation to the unstable indolenine **22**, a biomimetic Mannich type cyclization led to 19-oxoaspidofractinine (**2**), a direct precursor of aspidofractinine **6**.

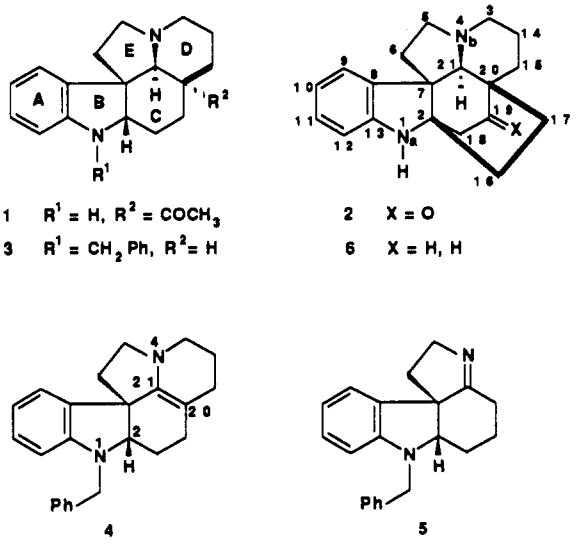
The *Aspidosperma* alkaloids belong to a series of natural products useful for the hemisynthesis of biologically active compounds (e.g. vincamine and antitumor dimeric alkaloids).[1] For these reasons increasing attention has been paid to their total synthesis.[2] In continuation of our program[3] aimed at the synthesis of the pentacyclic framework of these compounds, we report herein the synthesis of 19-oxoaspidospermidine (**1**) and 19-oxoaspidofractinine (**2**) (Chart I).

Our scheme is based on the fundamentally new approach we have described before for *N*-1-benzyldeethylaspidospermidine (**3**)[4] from *cis*-hexahydrocarbazol-4-ones.[5]

For the generality of this methodology it is necessary to be able to introduce a functionalized C-20[6] side chain often present in alkaloids of this group. The use of the previously described pentacyclic enamine **4**[4] failed due to its poor reactivity (no reaction occurred even with acetyl chloride). Starting from tetracyclic imine **5**[4] (Chart I), double alkylation at C-20 presented problems of reactivity and stereochemistry.

In order to circumvent these problems we thought that a tetracyclic enamine such as **11** (Scheme I) would be considerably more reactive than **4** and could be a useful synthetic intermediate.

Chart I



In our strategy the last stage of the synthesis is the formation of ring D. A C-20 acetyl chain would allow the

† Université Blaise Pascal.
‡ Faculté des Sciences Pharmaceutiques et Biologiques.

(1) The Monoterpenoid Indole Alkaloids. In *Heterocyclic Compounds*; Saxton, J. E., Ed.; Wiley: New York, 1983; Vol. 25.

0022-3263/90/1955-5483$02.50/0 © 1990 American Chemical Society