Aldol Reaction of Reducing Sugars. Convenient Stereoselective Synthesis of Ribofuranosylacetone and Chiral Dienones

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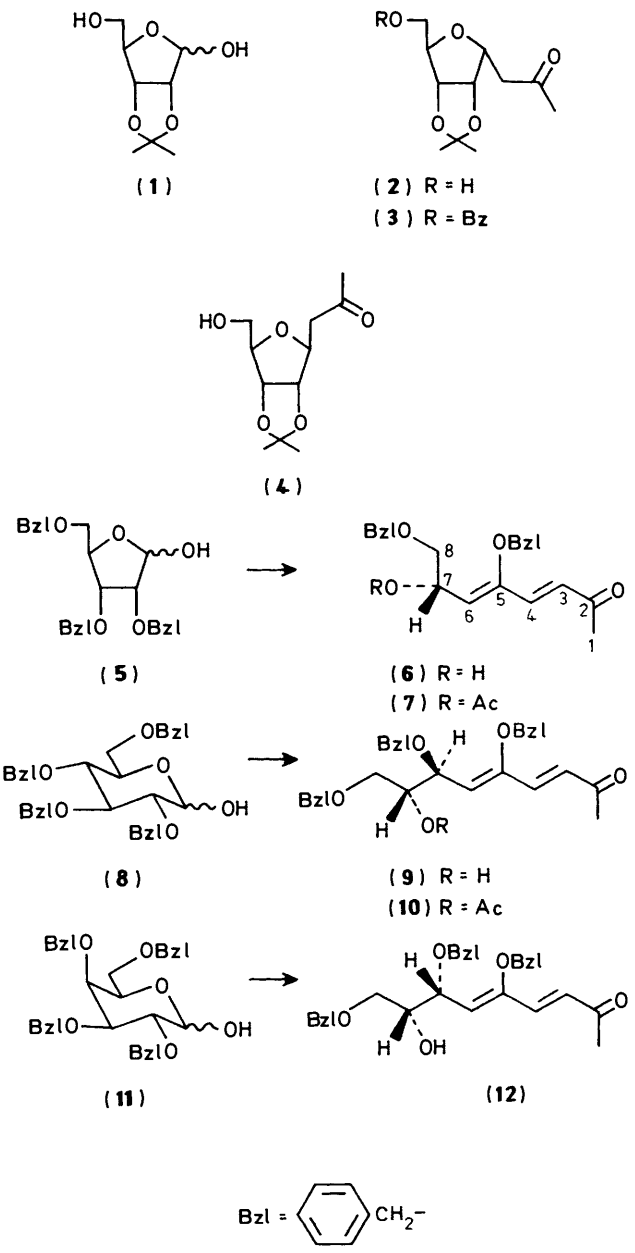
Aldol reaction of 2,3-*O*-isopropylidene-D-ribose with acetone, catalysed by aqueous K_2CO_3, gave 1-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)acetone. Similar reactions of 2,3,5-tri-*O*-benzyl-D-ribofuranose, 2,3,4,6-tetra-*O*-benzyl-D-gluco- and -D-galactopyranose afforded chiral (3*E*,5*Z*,7*S*)-octa 3,5-dien-2-one, (3*E*,5*Z*,7*S*,8*R*)-nona-3,5-dien-2-one, and (3*E*,5*Z*,7*R*,8*R*)-nona-3,5-dien-2-one derivatives, respectively.

C-Glycosyl derivatives[1] are useful chiral synthons for the total synthesis of natural products of biological and pharmaceutical importance.[2,3] The methods for their synthesis include: (a) the reaction of a glycosyl derivative, having a leaving group at the anomeric position, with a carbon nucleophile, such as cyanide ion,[1] a malonic-type carbanion,[4] a silane,[5] an organosilver reagent,[6] or an enol trimethylsilyl ether;[7,8] (b) the addition of carbon nucleophiles to glycals;[9] (c) the reaction of organolithium[10] or organomanganese[11] derivatives of sugars with electrophilic carbon centres; (d) the free-radical reaction of sugar halides with alkylstannanes.[12]

The aldehyde group of reducing sugars can also undergo a variety of reactions leading to the formation of new C–C bonds. The Wittig reaction,[13,14] the addition of organometallic (Li,[15] Mg[16]) reagents, and the reaction with nitromethane[17] have been extensively studied. The scarce reports on aldol and related reactions[18,†] include the Knoevenagel reaction with malonic-type derivatives.[19,20] Here we report a convenient and stereoselective synthesis of ribofuranosyl acetone and chiral dienones by aldol reaction of reducing sugars with acetone.

Reaction of 2,3-*O*-isopropylideneribose[21] (**1**) with acetone in the presence of aqueous K_2CO_3 afforded 4,7-anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-D-*altro*-2-octulose (**2**). This compound was characterised as its 8-*O*-benzoyl derivative (**3**). There is n.m.r. evidence that the two *C*-glycosyl epimers, the D-*altro* (**2**) and 4,7-anhydro-1,3-dideoxy-5,6-*O*-isopropylidene-D-*allo*-2-octulose (**4**) are formed in the reaction, but the thermodynamically more stable[13] D-*altro* stereoisomer (**2**) is the only detected final product. The configuration at C-4 of the octulose (**3**), was assigned based on the $J_{6,7} < 0.5$ Hz value, which indicates an 'α-anomeric configuration.'[13,22] D-*Altro*- and D-*allo*-octuloses related to (**2**) and (**4**) have been previously obtained as mixtures of diastereoisomers by Wittig reaction of ribose with acetylmethylene(triphenyl)phosphorane[14] and by reaction of 2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl fluoride with isopropenyl trimethylsilyl ether in the presence of BF_3.[8]

Application of the same procedure to reducing sugars having different hydroxy-protecting groups afforded different results. The benzyl-protected sugars 2,3,5-tri-*O*-benzyl-D-ribofuranose[23] (**5**), 2,3,4,6-tetra-*O*-benzyl-D-*gluco*-[24] (**8**) and -D-galactopyranose[25] (**11**) afforded α,β:γ,δ-unsaturated ketones (**6**), (**9**), and (**12**), respectively. These chiral, reactive intermediates result from the elimination of the 4-OH and 6-*O*-Bzl groups from the



† (*R*)- And (*S*)-2,3-*O*-isopropylideneglyceraldehyde have been extensively studied. See J. Jurczak, S. Pikul, and T. Bauer, *Tetrahedron*, 1986, **42**, 447.

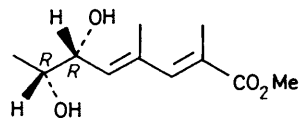
Table. N.O.e. values for compounds (**6**) and (**12**)

Compound	Proton irradiated	N.O.e.s observed at the indicated protons				
		1-H_3	3-H	4-H	6-H	8-H
(**6**)	4-H	2.6		−83	11.4	
	6-H			13.2	−93	3.3
(**12**)	4-H	2.5		−90	12.6	
	6-H			12.7	−97	3.0

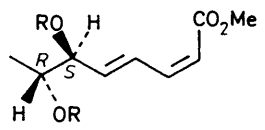
uloses formed by aldol reaction. Acetylation of compounds (**6**) and (**9**) with acetic anhydride–pyridine afforded the mono-acetylated derivatives (**7**) and (**10**), respectively.

The use of acetyl- and benzoyl-protected reducing carbohydrates as starting materials afforded complex mixtures. These were produced by partial deacylation, under the basic reaction conditions, on both reaction products and starting materials. The use of other bases such as NaOH, DBU, or NaH in the absence of water afforded mixtures from which the above compounds could also be identified.

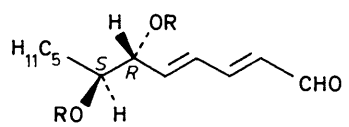
The stereochemistries of the C(3)–C(4) and C(5)–C(6) double bonds of (**6**), (**7**), (**9**), (**10**), and (**12**) are *E* and *Z*, respectively. The coupling constant $J_{3,4}$ 15.5—16 Hz indicated a *trans* relationship between 3-H and 4-H. The *Z* stereochemistry of the C(5)–C(6) double bond was inferred from ^{1}H nuclear Overhauser effect (n.O.e.) experiments,[22] which also confirmed the C(3)–C(4) assignment. The n.O.e. values (Table) indicated that 4-H is close to 6-H and -H_3, but not to 3-H. According to the spectral data, the structure of the dienone system is identical for (**6**), (**7**), (**9**), (**10**), and (**12**). This indicates that the stereochemistry of the two double bonds does not depend on the different absolute configurations at C-2 and C-3 of the ribo, gluco, and galacto structures of the starting sugars. However,



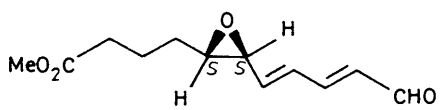
(**13**)



(**14**)



(**15**)



(**16**)

the stereochemistry of the chiral carbon atoms of these dienones is that of the same carbon atoms of the parent reducing sugars. α,β:γ,δ-Unsaturated carbonyl derivatives, such as (**13**),[26] (**14**),[27] (**15**),[28] and (**16**),[29] structurally related to those reported in this paper, have been used as key chiral synthons for the total synthesis of some natural products, such as citreoviridin, a potent neurotoxic mycotoxin, trichothecenes, lipoxin B, and leukotrienes C-1 and A_4, respectively.

Taking into account the variety of stereochemistries at C-4, C-5, and eventually at higher positions, of the possible starting reducing sugars, this reaction provides a method for the convenient and cheap preparation of chiral conjugated dienones of different lengths incorporating one or more asymmetric carbon atoms of defined absolute stereochemisty.

Experimental

Microanalyses were obtained with a Heraeus CHN-O-Rapid elemental analyser. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. ^{1}H N.m.r. spectra were recorded with a Bruker AM-200 or a Varian EM-390 spectrometer using Me_4Si as internal standard; mass spectra were recorded with a Vacuum Generators VG 12-250, i.r. spectra were obtained using a Shimadzu IR-435 spectrometer, and u.v. spectra were obtained using a Perkin-Elmer 550 SE spectrophotometer. Analytical t.l.c. plates were purchased from Merck, preparative t.l.c. was performed on glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck), flash column chromatography was performed with silica gel 60 230—400 mesh (Merck). Compounds were detected by u.v. light (254 nm) or by spraying the plates with 30% H_2SO_4 in ethanol, and heating.

Aldol Reaction of Reducing Sugars with Acetone. General Procedure.—A mixture of the reducing sugar (1 mmol), acetone (40 ml), water (5 ml), and K_2CO_3 (1.4 mmol) was heated to reflux with magnetic stirring for 12 h. The reaction mixture was evaporated to dryness. The residue was treated with water, and the mixture was extracted with chloroform (3 × 20 ml). The organic phase was dried with anhydrous Na_2SO_4, filtered, and concentrated to give a syrup, which was purified by flash column chromatography with hexane–ethyl acetate (2:1) as eluant.

4,7-*Anhydro*-8-O-*benzoyl*-1,3-*dideoxy*-5,6-O-*isopropylidene*-D-*altro*-2-*octulose* (**3**).—The syrup (**2**) (0.17 g, 75%), obtained by reaction of the furanose (**1**) with acetone according to the general procedure, was stirred with pyridine (15 ml) and benzoyl chloride (2 ml) at room temperature for 3 h. The reaction mixture was then concentrated under reduced pressure, the residue was dissolved in chloroform (50 ml), and the solution was washed successively with 1M HCl (10 ml) and water (2 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The syrupy residue was purified on preparative t.l.c. plates with hexane–ethyl acetate (3:1) as developer to afford the *title compound* (**3**) as a syrup [0.23 g, 69% total yield from (**1**)] (Found: C, 64.5; H, 6.8. $C_{18}H_{22}O_6$ requires C, 64.7; H, 6.6%); $[\alpha]_D$ +8° (*c* 0.5 in $CHCl_3$); $\nu_{max.}$(film) 1 725 cm^{-1} (C=O, $C_6H_5CO_2$); $\lambda_{max.}$(MeOH) 227 nm (ε 9 300 dm^3 mol^{-1} cm^{-1}); δ_H(200 MHz; $CDCl_3$) 1.33 and 1.50 (6 H, 2 s, isopropylidene), 2.20 (3 H, s, 1-H_3), 2.92 (2 H, m, 3-H_2), 4.24—4.43 (3 H, m, 7-H and 8-H_2), 4.47 (1 H, dt, $J_{3,4}$ 6.7, $J_{4,5}$ 4.0 Hz, 4-H), 4.78 (1 H, d, $J_{5,6}$ 6.2, $J_{6,7}$ <0.5 Hz, 6-H), and 4.88 (1 H, dd, 5-H); *m/z* 334 (M^+, 1.5%), 319 (M^+ − 15, 2), 318 (12), 277 (M^+ − CH_2COCH_3, 7).

(3E,5Z,7S)-5,8-*Dibenzyloxy*-7-*hydroxyocta*-3,5-*dien*-2-*one* (**6**).—Reaction of compound (**5**) according to the general procedure afforded the *title compound* (**6**) as a syrup (0.24 g, 68%) (Found: C, 74.6; H, 6.95. $C_{22}H_{24}O_4$ requires C, 74.9; H, 6.8%); $\nu_{max.}$(Nujol) 3 420 (OH) and 1 670 cm^{-1} (α,β:γ,δ-unsaturated ketone); $\lambda_{max.}$(MeOH) 275 nm (16 800); δ_H(200 MHz; $CDCl_3$) 2.25 (3 H, s, 1-H_3), 3.34 (2 H, m, 8-H_2), 4.50 and 4.80 (4 H, 2 s, $C_6H_5CH_2$), 4.70 (1 H, m, 7-H), 5.53 (1 H, d, $J_{6,7}$ 8.6 Hz, 6-H), 6.41 (1 H, d, $J_{3,4}$ 16 Hz, 3-H), and 6.93 (1 H, d, 4-H); *m/z* 352 (M^+, 0.4%), 337 (0.7), 309 (2), and 231 (23).

(3E,5Z,7S)-7-*Acetoxy*-5,8-*dibenzyloxyocta*-3,5-*dien*-2-*one* (**7**).—A solution of the alcohol (**6**) (0.352 g, 1 mmol), pyridine

(10 ml), and acetic anhydride (1 ml) was stirred at room temperature for 16 h. The solvents were evaporated off under reduced pressure, the residue was dissolved in chloroform (30 ml), and the solution was washed successively with 1M HCl (6 ml) and water (2 × 10 ml). The organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by flash column chromatography with hexane–ethyl acetate (5:2) as eluant to give the *acetate* (**7**) as a syrup (0.335 g, 85%) (Found: C, 72.8; H, 6.1. $C_{24}H_{26}O_5$ requires C, 73.0; H, 6.1%); $\nu_{max.}$(Nujol) 1 735 (acetate) and 1 670 cm^{-1} (α,β:γ,δ-unsaturated ketone); $\lambda_{max.}$(MeOH) 275 nm (15 900); δ_H(90 MHz; $CDCl_3$) 2.03 (3 H, s, OAc), 2.26 (3 H, s, 1-H_3), 3.52 (2 H, d, $J_{7,8}$ 5 Hz, 8-H_2), 4.50 (2 H, s, $C_6H_5CH_2$), 4.70 and 4.91 (2 H, AB system, J 10 Hz, $C_6H_5CH_2$), 5.50 (1 H, d, $J_{6,7}$ 8.5 Hz, 6-H), 5.93 (1 H, m, 7-H), 6.42 (1 H, d, $J_{3,4}$ 15.5 Hz, 3-H), and 6.90 (1 H, d, 4-H).

(3E,5Z,7S,8R)-5,7,9-*Tribenzyloxy*-8-*hydroxynona*-3,5-*dien*-2-*one* (**9**).—Reaction of compound (**8**) according to the general procedure afforded the *title product* (**9**) as a syrup (0.33 g, 70%) (Found: C, 76.5; H, 6.9. $C_{30}H_{32}O_5$ requires C, 76.2; H, 6.75%); $\nu_{max.}$(Nujol) 3 440 (OH) and 1 668 cm^{-1} (α,β:γ,δ-unsaturated ketone); $\lambda_{max.}$(MeOH) 276 nm (18 900); δ_H(200 MHz; $CDCl_3$) 2.25 (3 H, s, 1-H_3), 3.57 (2 H, m, 9-H_2), 3.91 (1 H, m, 8-H), 4.25 and 4.49 (2 H, AB system, J 10.5 Hz, $C_6H_5CH_2$), 4.43 (1 H, dd, 7-H), 4.46 and 4.72 (4 H, 2 s, $C_6H_5CH_2$), 5.57 (1 H, d, $J_{6,7}$ 9.2 Hz, 6-H), 6.41 (1 H, d, $J_{3,4}$ 15.5 Hz, 3-H), and 6.90 (1 H, d, 4-H); *m/z* 472 (M^+, 0.1%), 446 (16), 429 (4), 322 (14), 321 (32), and 231 (41).

(3E,5Z,7S,8R)-8-*Acetoxy*-5,7,9-*tribenzyloxynona*-3,5-*dien*-2-*one* (**10**).—Acetylation of the alcohol (**9**) (0.47 g, 1 mmol) with acetic anhydride (1 ml) and pyridine (10 ml) and work-up as described before for compound (**7**) afforded the *acetate* (**10**) as a syrup (0.425 g, 83%) (Found: C, 74.6; H, 6.85. $C_{32}H_{34}O_6$ requires C, 74.7; H, 6.6%); $\nu_{max.}$(Nujol) 1 735 (acetate) and 1 670 cm^{-1} (α,β:γ,δ-unsaturated ketone); $\lambda_{max.}$(MeOH) 276 nm (18 200); δ_H(90 MHz; $CDCl_3$) 1.97 (3 H, s, OAc), 2.22 (3 H, s, 1-H_3), 3.57 (2 H, d, $J_{8,9}$ 5 Hz, 9-H_2), 4.20 and 4.42 (2 H, AB system, J 10.5 Hz, $C_6H_5CH_2$), 4.43 and 4.67 (4 H, 2 s, $C_6H_5CH_2$), 4.60 (1 H, dd, 7-H), 5.14 (1 H, m, 8-H), 5.44 (1 H, d, $J_{6,7}$ 9.5 Hz, 6-H), 6.35 (1 H, d, $J_{3,4}$ 15.5 Hz, 3-H), and 6.89 (1 H, d, 4-H).

(3E,5Z,7R,8R)-5,7,9-*Tribenzyloxy*-8-*hydroxynona*-3,5-*dien*-2-*one* (**12**).—Reaction of compound (**11**) according to the general procedure afforded the *title product* (**12**) as a syrup (0.32 g, 69%) (Found: C, 76.35; H, 6.85. $C_{30}H_{32}O_5$ requires C, 76.15; H, 6.75%); $\nu_{max.}$(Nujol) 3 430 (OH) and 1 695 cm^{-1} (α,β:γ,δ-unsaturated ketone); $\lambda_{max.}$(MeOH) 277 nm (21 250); δ_H(200 MHz; $CDCl_3$) 2.26 (3 H, s, 1-H_3), 3.48 (2 H, d, $J_{8,9}$ 4.5 Hz, 9-H_2), 3.70 (1 H, m, 8-H), 4.23 and 4.50 (2 H, AB system, J 11.5 Hz, $C_6H_5CH_2$), 4.43 (1 H, dd, 7-H), 4.47 and 4.70 (4 H, 2 s, $C_6H_5CH_2$), 5.55 (1 H, d, $J_{6,7}$ 10 Hz, 6-H), 6.40 (1 H, d, $J_{3,4}$ 15.5 Hz, 3-H), and 6.95 (1 H, d, 4-H); *m/z* 472 (M^+, 0.1%), 429 (3), 322 (14), 321 (32), and 231 (47).

Nuclear Overhauser Effect Experiments.—^{1}H N.m.r. steady-state n.O.e. difference spectroscopy experiments were carried out on compounds (**6**) and (**12**) with a Bruker AM 200 spectrometer operating in the pulse mode. The standard Bruker microprogram library was used to perform sequential multiplet line irradiation.[30] Each irradiation multiplet frequency was cycled 20 times before acquisition. A total irradiation time of 2 s and an acquisition time of 2 s were used. Solutions ($CDCl_3$ + Me_4Si) were measured at 30 °C and a 90 ° lead pulse was used in all cases. The decoupling power was adjusted in order to obtain maximum saturation (80—90%) compatible with minimum frequency spill over to neighbouring multiplets. F.I.D.s were weighted with a 2 Hz exponential line-broadening factor, subtracted, and fourier transformed. N.O.e. values were calculated from integrals of the difference and control irradiation spectra.

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References

1 S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, 1976, **33**, 111.
2 S. Hanessian, 'Total Synthesis of Natural Products. The Chiron Approach,' Pergamon, Oxford, 1983.
3 T. D. Inch, *Tetrahedron*, 1984, **40**, 3161; B. Fraser-Reid and R. C. Anderson, *Fortschr. Chem. Org. Naturst.*, 1980, **39**, 1.
4 H. Ohrui, and J. J. Fox, *Tetrahedron Lett.*, 1973, 1951.
5 T. L. Cupps, D. S. Wise, and L. B. Townsend, *J. Org. Chem.*, 1982, **47**, 5115.
6 F. G. De las Heras, S. Y.-K. Tam, R. S. Klein, and J. J. Fox, *J. Org. Chem.*, 1976, **41**, 84.
7 T. Ogawa, A. G. Pernet, and S. Hanessian, *Tetrahedron Lett.*, 1973, 3543.
8 Y. Araki, K. Watanabe, F. H. Kuan, K. Itoh, N. Kobayashi, and Y. Ishido, *Carbohydr. Res.*, 1984, **127**, C-5.
9 R. D. Dawe and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1981, 1180.
10 J. M. Beau and P. Sinaÿ, *Tetrahedron Lett.*, 1985, **26**, 6185.
11 P. DeShong, G. A. Slough, and V. Elango, *J. Am. Chem. Soc.*, 1985, **107**, 7788.
12 G. E. Keck and J. B. Yates, *J. Am. Chem. Soc.*, 1982, **104**, 5829.
13 H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, 1975, **97**, 4602.
14 Yu. A. Zhdanov, Yu. E. Alexeev, and V. G. Alexeeva, *Adv. Carbohydr. Chem. Biochem.*, 1972, **27**, 227.
15 E. J. Corey, B. C. Pan, D. H. Hua, and D. R. Deardorff, *J. Am. Chem. Soc.*, 1982, **104**, 6816.
16 J. G. Buchanan, A. R. Edgar, and M. J. Power, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1943.
17 T. Sakakibara, T. Takamoto, T. Matsuzaki, H. Omi, U. W. Maung, and R. Sudoh, *Carbohydr. Res.*, 1981, **95**, 291.
18 C. H. Heathcock in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, 1984, vol. 3, part B, p. 111.
19 E. Breuer, D. Melumad, S. Sarel, E. Margalith, and E. Katz, *J. Med. Chem.*, 1983, **26**, 30.
20 F. J. Lopez-Herrera and M. S. Pino-González, *Carbohydr. Res.*, 1986, **152**, 283.
21 N. A. Hughes and P. R. H. Speakman, *Carbohydr. Res.*, 1965, **1**, 171; M. Kiso and A. Hasegawa, *ibid.*, 1976, **52**, 95.
22 M. A. Bernstein, H. E. Morton, and Y. Guindon, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1155.
23 R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, 1961, **26**, 4605.
24 C. P. J. Glaudemans and H. G. Fletcher, *Methods Carbohydr. Chem.*, 1972, **6**, 373.
25 P. W. Austin, F. E. Hardy, J. G. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1965, 1419.
26 B. M. Trost, J. K. Lynch, and S. R. Angle, *Tetrahedron Lett.*, 1987, **28**, 375.
27 D. B. Tulshian and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1981, **103**, 474; *J. Org. Chem.*, 1982, **47**, 3359.
28 J. Morris and D. G. Wishka, *Tetrahedron Lett.*, 1986, **27**, 803.
29 E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Sammelsson, and S. Hammarström, *J. Am. Chem. Soc.*, 1980, **102**, 1436.
30 M. Kinns and J. K. M. Sanders, *J. Magn. Reson.*, 1984, **56**, 518.

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