Dynamic ^{1}H Nuclear Magnetic Resonance Spectroscopic Studies of Complexes formed between Substituted Ammonium Cations and two Chiral Diaza-crown Ethers incorporating Asymmetric Carbohydrate Units

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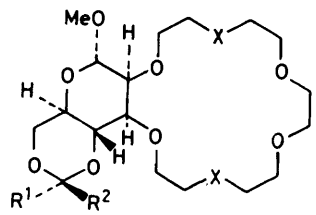
Two diaza-18-crown-6 derivatives (**1**) and (**2**), incorporating methyl 4,6-*O*-benzylidene- and methyl 4,6-*O*-[(*S*)-phenylethylidene]-α-D-mannopyranosidic residues, have been shown, by variable-temperature high-field ^{1}H n.m.r. spectroscopy, to form strong anisometric 1:1 complexes with substituted ammonium cations in CD_2Cl_2 solutions. Although there are a few examples of almost equally populated anisometric complexes, in most cases the major complex is associated with the β-face of the macrocyclic ring. Relevant thermodynamic data have been obtained from integration of appropriate signals in the low-temperature spectra. Approximate kinetic data have been evaluated using appropriate equations for site exchange between unequally populated sites.

The design and synthesis[1-4] of chiral molecular receptors has been of crucial importance to (i) the growth of the branch of separation science[5] concerned with the chiral discrimination of enantiomers and (ii) the development of novel approaches to enantioselective synthesis depending on enantiomer[6] (kinetic resolution) and enantioface[7] differentiation.

N.m.r. spectroscopy provides[8-10] an indispensible means of probing the nature of complexes. Although advanced techniques (*e.g.* nuclear Overhauser effect experiments[11] and ^{13}C spin–lattice relaxation time measurements[12]) can often provide a deeper insight into the dynamic stereochemistry associated with complex formation, dynamic n.m.r. spectroscopy[13] is particularly well suited[8-10] to investigating the thermodynamics and kinetics of complexation processes. Chiral crown ether receptors incorporating asymmetric carbohydrate residues[14-17] are particularly useful for studying their complexing behaviour with substituted ammonium cations (RNH_3^+ ions) by variable-temperature ^{1}H n.m.r. spectroscopy. Often, anisometric[18] complexes[9] can be identified at low temperatures and their equilibrium proportions estimated from integration of appropriate signals: assuming that the site-exchange processes are governed[19] by a unimolecular dissociative–recombination mechanism,[20] the free energies of activation for dissociation of the complexes can be easily estimated by dynamic ^{1}H n.m.r. spectroscopy. Such thermodynamic and kinetic data obtained for anisometric complexes in solution can be useful[14] in identifying and estimating the quantitative importance of weak noncovalent bonds (*e.g.* dipole-induced dipole interactions[11,21]) between substrates and their receptors. So far, detailed investigations[9,14] have been carried out on asymmetric 'all-oxygen' 18-crown-6 derivatives incorporating glycosidic residues with the α- and β-D-*gluco*-, α- and β-D-*galacto*-, α-D-*manno*-, and α-D-*altro*-configurations.

In general, the complexing behaviour of chiral aza-crown ethers has been investigated[4,22-25] to a much lesser extent than that of their 'all-oxygen' counterparts. In this paper, we report on the dynamic ^{1}H n.m.r. spectroscopic investigations of the 1:1 complexes formed between some RNH_3^+ ions and two asymmetric diaza-18-crown-6 derivatives (**1**)[26] and (**2**),[27] incorporating methyl 4,6-*O*-benzylidene-α-D-mannopyranosidic and methyl 4,6-*O*-[(*S*)-phenylethylidene]-α-D-mannopyranosidic units, respectively. The aim of the present investigation was to discover if complexation of RNH_3^+ ions could be directed



	X	R^1	R^2
(1)	NMe	Ph	H
(2)	NMe	Me	Ph
(3)	O	Ph	H

exclusively to either the α- or the β-face[9,14] (Figure) of the macrocyclic rings in receptor molecules such as (**1**) and (**2**).

Results and Discussion

From an inspection of the stereochemical representations of receptors (**1**) and (**2**) shown in their probable complexing conformations (*cf.* ref. 14) in the Figure, it is obvious that the main structural difference is associated with the orientation of the phenyl group on the acetal carbon atom. In (**1**), the phenyl group is equatorial and approximately orthogonal to the mean plane of the macrocyclic ring; in (**2**), the phenyl group is axial and oriented over the β-face of the macrocycle.

Low-temperature ^{1}H n.m.r. spectra were recorded for solutions in CD_2Cl_2 at 220 MHz. The influence of temperature on the chemical shifts of protons in the free receptors was not remarkable: nor was there any evidence for conformationally dictated exchange processes, at least down to −100 °C. The chemical-shift changes with the temperature for some selected ^{1}H probes in the free receptors are listed in Table 1. The temperature dependence of the ^{1}H n.m.r. spectra of 1:1 complexes formed between receptors (**1**) and (**2**) and a wide range of RNH_3^+ salts were investigated. The anomeric (H-1), benzylidene methine (PhC*H*), phenylethylidene methyl ($PhCH_3$), and *N*-methyl (NCH_3) protons proved to be highly convenient ^{1}H n.m.r. probes since they all gave rise to characterisable signals usually well separated from other signals in the spectra: their singlet, or near singlet, character was also a

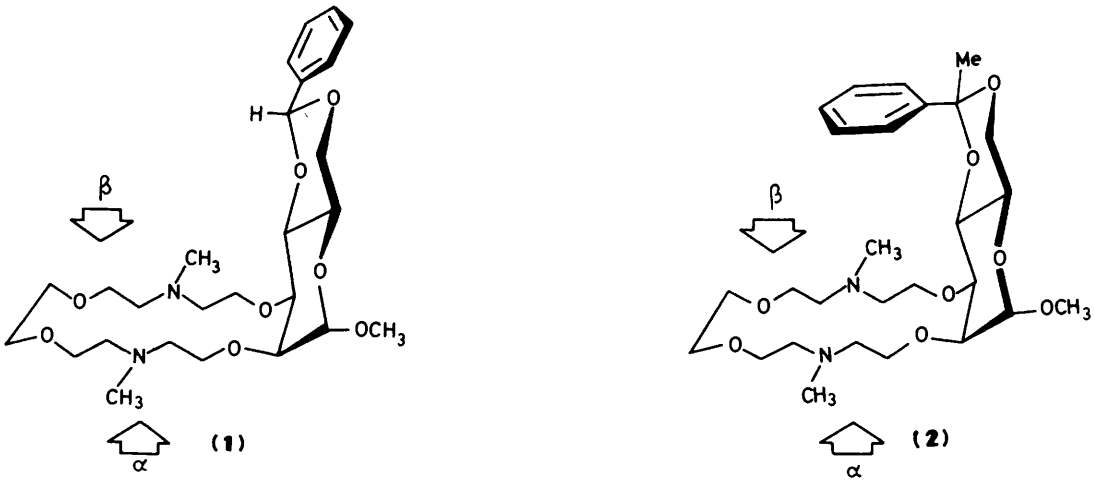


Figure. The stereochemical differences associated with the acetal ring: α- and β-approaches to the macrocyclic rings of receptors (**1**) and (**2**)

Table 1. ^{1}H N.m.r. chemical shifts (δ) (solvent CD_2Cl_2) for the selected probes in the free receptors at various temperatures

	Receptor (1)					Receptor (2)			
Probe	+20 °C	−40 °C	−60 °C	−80 °C	−100 °C	+20 °C	−40 °C	−60 °C	−80 °C
PhCC*H*$_3$						1.44	1.46	1.48	1.48
NC*H*$_3$	2.22	2.21	2.20	2.20	2.19	2.17	2.19	2.20	2.18
NC*H*$_3$	2.30	2.31	2.31	2.32	2.32	2.30	2.28	2.27	2.24
OC*H*$_3$	3.37	3.38	3.39	3.40	3.41	3.27	3.29	3.30	3.30
H-1	4.71	4.76	4.80	4.81	4.82	4.54	4.60	4.64	4.67
PhC*H*	5.59	5.62	5.63	5.64	5.65				

Table 2. ^{1}H N.m.r. chemical shifts (δ) (solvent CD_2Cl_2) for H-1, PhC*H*, and PhCC*H*$_3$ at −80 °C, and for NC*H*$_3$ at +20 °C in the 1 : 1 complexes of the receptors (**1**) and (**2**) with RNH_3X

	Receptor (1)				Receptor (2)			
RNH_3X	H-1	PhC*H*	NC*H*$_3$	NC*H*$_3$	H-1	PhCC*H*$_3$	NC*H*$_3$	NC*H*$_3$
$MeNH_3BPh_4$	5.00 mjr 4.90 min	5.58 mjr 5.50 min	2.12	2.01	4.93 mjr 4.80 min	1.57	2.24	1.98
$Pr^nNH_3BPh_4$					4.92 min 4.82 mjr	1.53	2.27	2.07
$Bu^tNH_3BPh_4$	5.01	5.50	2.21	2.07	4.92	1.52	2.18	2.09
$Bu^tNH_3ClO_4$	5.03	5.49	2.30	2.13				
$PhCH_2NH_3BPh_4$	5.05 min 5.10 mjr	4.86 mjr 4.96 min	2.18	2.01	4.86 mjr 4.97 min	1.53	2.27	1.81
(*R*)-$PhCHMeNH_3BPh_4$	5.07 mjr 4.96 min	5.31	2.06	1.97	4.84	1.56	2.15	1.88
(*S*)-$PhCHMeNH_3BPh_4$	5.10 mjr 4.95 min	5.65	2.05	1.96	4.83 mjr 4.60 min	1.50	2.15	1.85
(*R*)-$PhCH_2CH(CO_2Me)NH_3ClO_4$	5.13 mjr 4.98 min	5.62	2.46	2.20	4.77	1.53	2.62	2.44
$MeO[CH_2]_2NH_3BPh_4$	4.97 4.90	br	2.10	2.02	4.98 mjr 4.84 min	1.57	2.26	2.06
$HO[CH_2]_2NH_3BPh_4$	4.92 mjr 5.00 min	5.83 min 5.68 mjr	2.08	1.97	4.94 min 4.82 mjr	1.53	2.30	2.08
$HO[CH_2]_3NH_3BPh_4$	5.00 4.90	5.58	2.13	2.04	4.98 mjr 4.83 min	1.57	2.27	2.06
$HOCH_2CMe_2NH_3BPh_4$	4.96 5.03	5.59	2.20	2.03	4.97 mjr 4.90 min	1.54	2.24	2.12

Table 3. Kinetic and thermodynamic data for the dissociation of the more stable complex in CD_2Cl_2 solutions.

	Receptor (1)			Receptor (2)		
RNH_3X	Complex ratio mjr:min	$k^a_{mjr\rightarrow min}$ (T/K) / s^{-1}	$\Delta G^{\ddagger a}_{mjr\rightarrow min}$ / kJ mol^{-1} (kcal mol^{-1})	Complex ratio mjr:min	$k^a_{mjr\rightarrow min}$ (T/K) / s^{-1}	$\Delta G^{\ddagger a}_{mjr\rightarrow min}$ / kJ mol^{-1} (kcal mol^{-1})
$MeNH_3BPh_4$	83:17					
$Pr^nNH_3BPh_4$				77:23	10.7 (178)	39 (9.3)
$Bu^tNH_3BPh_4$				87:13	10.2 (213)	47 (11.2)
$Bu^tNH_3ClO_4$						
$PhCH_2NH_3ClO_4$[b]	82:18	3.67 (208)	48 (11.5)	79:21	6.9 (213)	48 (11.4)
(*R*)-$PhCHCH_3NH_3BPh_4$	85:15	5.02 (193)	44 (10.5)			
(*S*)-$PhCHCH_3NH_3BPh_4$	70:30	10.4 (203)	45 (10.7)	91:9	10.7 (193)	43 (10.2)
(*R*)-$PhCH_2CH(CO_2Me)NH_3ClO_4$	78:22	17.2 (193)	42 (10.0)			
$HO[CH_2]_2NH_3BPh_4$	59:41	33[c] (223)	47 (11.2)	70:30	10.7 (193)	43 (10.2)
$HO[CH_2]_3NH_3BPh_4$				66:34	10.7 (213)	47 (11.2)
$HOCH_2CMe_2NH_3BPh_4$				57:43	33[c] (213)	45 (10.7)

[a] The exchange rate constant was calculated (J. Sandström, 'Dynamic NMR Spectroscopy,' Academic Press, London, 1982, p. 85) at the temperature given in parentheses using the approximate expression $k_{mjr\rightarrow min} = \pi(W^* - W)$, where W^* is the bandwidth of the major signal in the region of line-broadening by exchange and W corresponds to the bandwidth of this signal in the slow exchange limit. The free energy of activation ($\Delta G^{\ddagger}_{mjr\rightarrow min}$) was obtained from $k_{mjr\rightarrow min}$ using the Eyring equation. [b] Data were obtained from spectra recorded at 400 MHz with a Bruker WH400 spectrometer. [c] Since the signals relating to the protons undergoing exchange are almost equal, $k_{mjr\rightarrow min}$ was assumed to a first approximation to be given by the expression (ref. 13), $k_c = \pi\Delta\nu/2^{\frac{1}{2}}$, where k_c is the rate constant at the coalescence temperature (which is cited in parentheses) and $\Delta\nu$ is the frequency separation of the two signals in the slow exchange limit.

useful feature. Other signals with their associated multiplicities proved far less diagnostic of complex formation. The chemical shift differences between the ^1H probes in the free receptors and in their 1:1 complexes were invariable significant in all cases, thus indicating the formation of strong 1:1 complexes. The most dramatic changes were observed for the H-1, PhC*H*, and NCH_3 signals. Although the chemical shifts of the NCH_3 protons were highly temperature dependent, they were usually found to be overlapping with multiplets for the NCH_2 protons at low temperatures.

Table 2 records the chemical shifts observed in numerous 1:1 complexes for H-1, PhC*H*, and PhC*H*$_3$ at −80 °C as well as for NCH_3 at +20 °C. As in the case of the 'all-oxygen' 18-crown-6 derivative (**3**), incorporating a methyl 4,6-*O*-benzylidene-α-D-mannopyranosidic residue, the signals for H-1 in the 1:1 complexes of receptors (**1**) and (**2**) were shifted downfield (by 0.16—0.32 p.p.m.). Since the pyranosidic ring oxygen atom could become involved in the stabilisation of the 1:1 complex formed to the β-face of the macrocycle, the signal with the greater downfield shift was tentatively assigned to the 1:1 complex formed to the β-face. Depending on the nature of the substituted RNH_3^+ ion, significant shifts were also observed for PhC*H* in the 1:1 complexes: usually, but not always, these shifts were to higher field.

Table 3 lists these relative populations as well as the rate constants for dissociation of the more stable complexes calculated by an approximate procedure. The derived free energies of activation for dissociation indicate that the binding abilities of the receptors (**1**) and (**2**) for the RNH_3^+ ions investigated are very similar.

The following conclusions can be drawn from these investigations. The replacement of the two oxygen atoms in (**3**) by the two NCH_3 groups to afford receptor (**1**) has had little influence on (i) the strengths of binding of RNH_3^+ ions or (ii) the selectivity of binding to either the α- or the β-face of the macrocycle. Altering the orientation of the phenyl group on the 4,6-*O*-benzylidene ring in (**1**) and (**2**) from equatorial to axial also failed to influence the binding selectivity for RNH_3^+ ions at the α- and β-faces. Clearly, another receptor design and synthetic approach is required if binding of RNH_3^+ ions is to be directed exclusively to either face of 18-crown-6 derivatives incorporating asymmetric carbohydrate units.

Experimental

Compounds (**1**) and (**2**) were prepared according to the literature procedures.[26,27] Samples (*ca.* 10 mg) of the receptors (**1**) and (**2**) were dissolved in CD_2Cl_2 (*ca.* 0.5 ml) and equimolar amounts of the RNH_3^+ salts were added. Rapid dissolution of the salts indicated instant formation of the complex. The ^1H n.m.r. spectra, unless otherwise stated, were recorded at 220 MHz with a Perkin-Elmer R34 spectrometer with tetramethylsilane as 'lock' and internal standard.

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References

1 D. J. Cram and J. M. Cram, *Acc. Chem. Res.*, 1978, **11**, 8; D. J. Cram and K. N. Trueblood, *Top. Curr. Chem.*, 1981, **98**, 43.
2 J.-M. Lehn, *Pure Appl. Chem.*, 1978, **50**, 871; 1979, **51**, 979; R. C. Hayward, *Chem. Soc. Rev.*, 1983, **12**, 285.
3 R. M. Kellogg, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 782.
4 D. A. Laidler and J. F. Stoddart, in 'The Chemistry of Functional Groups. Suppl. E. The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and their Sulphur Analogues. Part 1,' ed. S. Patai, Wiley-Interscience, Chichester, 1980, p. 1; J. F. Stoddart, *Prog. Macrocycl. Chem.*, 1981, **2**, 173; T. H. Crawshaw, D. A. Laidler, J. C. Metcalfe, R. B. Pettman, J. F. Stoddart, and J. B. Wolstenholme, in 'Chemical Approaches to Understanding Enzyme Catalysis,' eds. B. S. Green, Y. Ashani, and D. Chipman, Elsevier, Amsterdam, 1982, p. 49.
5 D. J. Cram, *Science*, 1974, **183**, 803; in 'Applications of Biomedical Systems in Chemistry,' eds. J. B. Jones, C. H. Sih, and D. Perlman, Wiley-Interscience, New York, 1967, vol. V, p. 815; L. R. Sousa, G. D. Y. Sogah, D. H. Hoffman, and D. J. Cram, *J. Am. Chem. Soc.*, 1978, **100**, 4569; G. D. Y. Sogah and D. J. Cram, *ibid.*, 1979, **101**, 3035; M. Newcomb, J. L. Toner, R. C. Helgeson, and D. J. Cram, *ibid.*, p. 4941; D. W. Curtis, D. A. Laidler, J. F. Stoddart, and G. H.

Jones, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1756; G. R. Weismann, *Asymm. Synth.*, 1983, **1**, 153.
6 Y. Chao and D. J. Cram, *J. Am. Chem. Soc.*, 1976, **98**, 1015; Y. Chao, G. R. Weismann, G. D. Y. Sogah, and D. J. Cram, *ibid.*, 1979, **101**, 4948; J.-M. Lehn and C. Sirlin, *J. Chem. Soc., Chem. Commun.*, 1978, 949; T. Matsui and K. Koga, *Tetrahedron Lett.*, 1979, 1115; *Chem. Pharm. Bull.*, 1979, **27**, 2295; S. Saski and K. Koga, *Heterocycles*, 1979, **12**, 1305; D. J. Cram and H. E. Katz, *J. Am. Chem. Soc.*, 1983, **105**, 135.
7 J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, 1979, **101**, 2759; P. Jouin, C. B. Troostwijk, and R. M. Kellogg, *ibid.*, 1981, **103**, 2091; G. D. Y. Sogah and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 1981, 625; B. L. Allwood, H. Shahriari-Zavareh, J. F. Stoddart, and D. J. Williams, *ibid.*, 1984, 1461.
8 S. J. Leigh and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1975, 414; *J. Chem. Soc., Perkin Trans. 1*, 1979, 1089; D. J. Pearson, S. J. Leigh, and I. O. Sutherland, *ibid.*, p. 3113.
9 J. F. Stoddart, *Chem. Soc. Rev.*, 1979, **8**, 85.
10 S. L. Baxter and J. S. Bradshaw, *J. Heterocycl. Chem.*, 1981, **18**, 233.
11 S. E. Fuller, B. E. Mann, and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1982, 1096; H. M. Colquhoun, S. M. Doughty, J. F. Stoddart, and D. J. Williams, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 235.
12 J.-P. Kintzinger, F. Kotzyba-Hibert, J.-M. Lehn, A. Pagelot, and K. Saigo, *J. Chem. Soc., Chem. Commun.*, 1981, 3833; D. S. B. Grace and J. Krane, *J. Chem. Res. (S)*, 1983, 192; L. Echegogen, G. W. Gokel, and A. Kaifer, *Tetrahedron Lett.*, 1982, **23**, 4449; D. M. Dishong, R. A. Schultz, and G. W. Gokel, *J. Org. Chem.*, 1982, **47**, 3195; L. Echegogen, A. Kaifer, H. D. Durst, and G. W. Gokel, *ibid.*, 1984, **49**, 688.
13 G. Binsch, *Top. Stereochem.*, 1968, **3**, 97; I. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, 1971, **4**, 71; S. F. Lincoln, *Prog. React. Kinet.*, 1977, **9**, 1; J. Sandström, 'Dynamic NMR Spectroscopy,' Academic Press, London, 1982.
14 D. A. Laidler and J. F. Stoddart, *Carbohydr. Res.*, 1977, **55**, C1; *J. Chem. Soc., Chem. Commun.*, 1977, 481; A. C. Coxon, D. A. Laidler, R. B. Pettman, and J. F. Stoddart, *J. Am. Chem. Soc.*, 1978, **100**, 8260; R. B. Pettman and J. F. Stoddart, *Tetrahedron Lett.*, 1979, 457, 461; D. A. Laidler, J. F. Stoddart, and J. B. Wolstenholme, *ibid.*, p. 465; H. Shahriari-Zavareh, J. F. Stoddart, M. K. Williams, B. L. Allwood, and D. J. Williams, *J. Incl. Phenom.*, in the press.
15 L. Tōke, L. Fenichel, P. Bakó, and J. Szejtli, *Acta Chim. Acad. Sci. Hung.*, 1978, **98**, 357; P. Bakó, L. Fenichel, L. Tōke, and M. Czugler, *Liebigs Ann. Chem.*, 1981, 1163; M. Czugler, *Cryst. Struct. Commun.*, 1981, **10**, 511; P. Bakó, L. Fenichel, and L. Tōke, *Acta Chim. Acad. Sci. Hung.*, 1982, **111**, 297.
16 W. Hain, R. Lehnert, H. Rottele, and G. Schröder, *Tetrahedron Lett.*, 1978, 625; W. Hain, R. Lehnert, B. Walz, and G. Schröder, *Liebigs Ann. Chem.*, 1984, 1046.
17 K. Suwińska, M. Pietraszkiewicz, J. Lipkowski, J. Jurczak, G. D. Andreetti, and G. Bocelli, *J. Mol. Struct.*, 1981, **75**, 221; K. Suwińska and G. D. Andreetti, *J. Incl. Phenom.*, 1983, **1**, 71.
18 K. Mislow, *Bull. Soc. Chim. Belges*, 1977, **86**, 595; J. Reisse, R. Ottinger, P. Bickart, and K. Mislow, *J. Am. Chem. Soc.*, 1978, **100**, 911.
19 M. R. Johnson, I. O. Sutherland, and R. F. Newton, *J. Chem. Soc., Perking Trans. 1*, 1979, 357.
20 F. de Jong, D. N. Reinhoudt, C. J. Smit, and R. Huis, *Tetrahedron Lett.*, 1976, 4783; F. de Jong, D. N. Reinhoudt, and R. Huis, *ibid.*, 1977, 3985; F. de Jong and D. N. Reinhoudt, *Adv. Phys. Org. Chem.*, 1980, **17**, 279.
21 D. A. Laidler and J. F. Stoddart, *Tetrahedron Lett.*, 1979, 453; J. F. Stoddart, in 'Enzymic and Non-enzymic Catalysis,' eds. P. Dunnill, A. Wiseman, and N. Blakebrough, Ellis-Horwood, Chichester, 1980, p. 84; in 'Lectures in Heterocyclic Chemistry,' eds. R. N. Castle and S. W. Schneller, 1980, vol. 5, p. S47.
22 D. A. Laidler and J. F. Stoddart, *J. Chem. Soc., Chem. Commun.*, 1976, 979.
23 D. J. Chadwick, I. A. Cliffe, and I. O. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1981, 992; D. J. Chadwick, I. A. Cliffe, R. F. Newton, and I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1707.
24 J. S. Bradshaw, B. A. Jones, R. B. Davidson, J. J. Christensen, J. D. Lamb, R. M. Izatt, F. G. Morin, and D. M. Grant, *J. Org. Chem.*, 1982, **47**, 3362; R. B. Davidson, J. S. Bradshaw, B. A. Jones, N. K. Dalley, J. J. Christensen, and R. M. Izatt, *ibid.*, 1984, **49**, 353.
25 M. Pietraszkiewicz, P. Satanski, and J. Jurczak, *J. Chem. Soc., Chem. Commun.*, 1983, 1184.
26 M. Pietraszkiewicz and J. Jurczak, *J. Chem. Soc., Chem. Commun.*, 1983, 132; *Tetrahedron*, 1984, **40**, 2967.
27 M. Pietraszkiewicz and J. Jurczak, *J. Carbohydr. Chem.*, in the press.

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