Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 689–703

TETRAHEDRON: *ASYMMETRY*

Stereochemistry of addition of carbanion reagents to 'diacetone fructose aldehyde'. Configurational assignment of a 1-deoxyheptulose derivative by X-ray crystallography and NMR studies directed to the assignment of isomeric adducts

Michael J. Costanzo, Libuse Jaroskova, Diane A. Gauthier and Bruce E. Maryanoff *

Drug Discovery, The R.W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477, USA

Received 23 November 1998; accepted 20 January 1999

Abstract

The addition of carbanionic reagents to 'diacetone fructose aldehyde' (**6**) was investigated with a focus on the stereocontrol. The Grignard reagents, MeMgBr, EtMgBr, *i*-PrMgBr, and MeMgI, gave a high bias (≥90%) for one diastereomer, assigned as the *R*-isomer, in ether at −78 to 0°C. The reaction of PhMgBr showed diminished diastereoselectivity under these conditions, with a significant dependence of the isomer ratio on temperature and solvent. $PhCH_2MgBr$ only afforded the adduct of 'allylic rearrangement', namely **13**, with poor diastereocontrol (ca. 60:40). MeLi, *t*-BuLi, PhLi, and $LiCH_2CO_2$-*t*-Bu provided adducts of **6** enriched in the *R*-isomer in the range of 80–89%, whereas 2-lithio-2-ethyl-1,3-dithiane gave a 94:6 ratio of *R*:*S* adducts (**15a**:**15b**). The *R* absolute stereochemistry at the carbinol C1 center of **4a** was established through X-ray analysis of sulfamate derivative **2a**. Carbon-13 NMR chemical shift criteria (the chemical shifts for C1 and C3) were identified to facilitate the stereochemical assignment of C1 adducts of **6**.

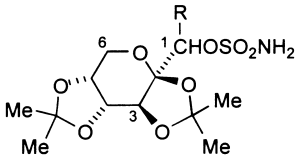
1. Introduction

Topiramate (**1**, Topamax®), an anti-convulsant discovered in our laboratories around 1980, is an important anti-epileptic drug that is marketed in many countries worldwide.[1] Within the broad scope of anti-convulsant agents, topiramate possesses a unique sugar sulfamate structure and a special combination of biological mechanisms of action.[1,2] As part of an analogue project, we had occasion to synthesize and test compounds substituted at the C1 position with methyl (**2**) and ethyl (**3**) groups.[3] Despite the fact that **2** and **3** had greatly attenuated anti-convulsant activity,[3b] it was interesting to note that the precursor alcohols (**4** and **5**) were formed from 'diacetone fructose aldehyde' (**6**) with a strong bias for one diastereomer (16:1

* Corresponding author. E-mail: bmaryano@prius.jnj.com

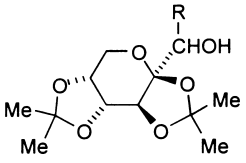
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00035-X

and 5:1, respectively; in THF:ether). Analysis of the ^{1}H and ^{13}C NMR spectroscopic data would not permit an assignment of stereochemistry to the new stereogenic center, because there was no precedent established.[3a]



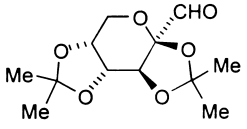
1 R = H
2 R = Me
3 R = Et

Configuration at C_1 when R ≠ H: **a** = *R*; **b** = *S*



4 R = Me
5 R = Et
7 R = EtC(O)
8 R = CH_2CO_2Me
9 R = CH_2CO_2-*t*-Bu
10 R = H

11 R = *i*-Pr
12 R = $PhCH_2$
13 R = *o*-tolyl
14 R = Ph
15 R = EDT
16 R = *t*-Bu



6

In 1981, Heathcock et al. reported the preparation of alcohol adducts **5** and **7** via the addition of EtMgBr (THF:ether, 0°C) and 2-lithio-2-ethyl-1,3-dithiane (THF:hexane, ca. −60°C) to **6**, with exclusive formation of one diastereomer, depicted in their paper with the *R* configuration at the newly formed stereogenic center.[4] However, this stereochemical assignment must be considered as arbitrary because no supporting evidence, spectroscopic or otherwise, was provided.[5] Around the same time (1980), Martinez et al. reported the addition of MeMgI to **6** in ether to obtain alcohols **4**, although they also did not assign the two diastereomers.[6] Interestingly, they observed that the ratio of diastereomeric alcohols **4** was temperature dependent, with formation of a single isomer at ca. 23°C and a ca. 60:40 ratio at 35°C (enriched in the first isomer). Recently, Izquierdo et al. found that reaction of **6** with methyl bromoacetate and zinc (dioxane, 23°C; modified Reformatsky conditions) or with lithio *tert*-butyl acetate (THF:ether:hydrocarbons, −78°C) resulted in adducts **8** or **9** with high selectivity for the diastereomer with the *R* configuration at the new stereocenter (ca. 10:1 and ca. 5:1, respectively).[7] Their 1997 paper provided the first stereochemical assignment for a carbanion addition product from **6**, based on unambiguous stereochemical correlation.[8]

Concurrent with the work of Izquierdo et al.,[7] we established the *R* configuration for the major isomer from the reaction of **6** with MeMgBr, i.e., **4a**, by X-ray crystallography of the sulfamate derivative, **1a**.[3a] In this paper, we report the details of our X-ray analysis of **1a**. Moreover, we describe results from a series of experiments involving the addition of carbanionic reagents to **6**, which serve to define the scope of the diastereocontrol, as well as the effects of temperature and solvent. Given the variety of diastereomeric pairs of carbinols on hand, we obtained extensive proton and carbon-13 NMR data, which has led to a spectroscopic criterion for the assignment of stereochemistry to such derivatives.

2. Results and discussion

*2.1. Addition of carbanion reagents to **6***

Subsequent to our initial work,[3a] we undertook a systematic investigation of the addition of simple Grignard reagents to aldehyde **6**. Our results with MeMgBr, EtMgBr, *i*-PrMgBr, $PhCH_2MgBr$, and PhMgBr are shown in Table 1. For MeMgBr, EtMgBr, *i*-PrMgBr, and PhMgBr, we examined five temperatures in the range from −78 to 35°C to define the effect of temperature on the stereochemistry. The reactions were generally conducted in anhydrous ether, except that MeMgBr was also studied in ether:THF (1:1) for continuity with our earlier experience.[3a]

Table 1
Reaction of carbanion reagents with **6**

Entry	Reagent[a]	Temp, °C	Yield of adducts[b]	Unreacted aldehyde[b]	Isomer ratio (*R*:*S*)[b]	Reduced product **10**[b]
1	MeMgBr	-78	85	10.7	98:2	
2	"	-20	90	5.8	97:3	
3	"	0	80	5.7	94:6	
4	"	20	95	4.6	91:9	
5	"	35	95	3.4	91:9	
6	MeMgBr[c]	0	93	2.1	93:7	
7	MeMgBr[d]	-78	90	7.4	98:2	
8	"	0	90	6.5	93:7	
9	"	35	93	3.5	89:11	
10	EtMgBr	-78	76	14.8	98:2	6.7
11	"	-20	83	7.2	96:4	7.3
12	"	0	75	6.2	94:6	7.5
13	"	20	83	4.2	91:9	9.9
14	"	35	90	2.5	89:11	11
15	*i*-PrMgBr	-78	50	15.3	98:2	31
16	"	-20	46	7.8	93:7	41
17	"	0	44	8.6	90:10	42
18	"	20	48	3.6	87:13	44
19	"	35	50	2.3	86:14	47
20	$PhCH_2MgCl$	-20[e]	20[f]	52	62:38[g]	
21	"	35	69[f]	9.7	63:37[g]	
22	PhMgBr	-78	80	8.0	89:11	
23	"	-20	89	5.4	82:18	
24	"	0	91	6.2	79:21	

Table 1 (continued)

Entry	Reagent[a]	Temp, °C	Yield of adducts[b]	Unreacted aldehyde[b]	Isomer ratio (*R*:*S*)[b]	Reduced product **10**[b]
25	"	20	94	2.7	76:24	
26	"	35	97	1.4	74:26	
27	PhMgBr/THF	-78	84	8.6	64:36	
28	PhMgBr/PhMe	-78	90	4.1	46:54	
29	MeLi	-78	83	10	89:11	
30	PhLi	-78	60	10	80:20	
31	*t*-BuLi	-78	30	17	87:13	18
32	$LiCH_2CO_2$-*t*-Bu[i]	-78	87	4.6	80:20	
33	$BrZnCH_2CO_2Me$[j]	*h*	80	4.8	90:10	
34	Li-2-Et-1,3-dithiane[k]	-70 to 23	65	13.7	94:6[l]	

a. All reactions were conducted in ethyl ether for 2 h with aldehyde **6** at 1 mM concentration and with 2.0 mol equiv of carbanion reagent, except as noted otherwise.

b. Determined by GLC analysis of crude product. The identity of each isomer was confirmed by isolation in a highly enriched state (see Experimental).

c. 5.0 mol equiv of MeMgBr.

d. 1:1 THF/ether.

e. Reacted for 4 h.

f. Abnormal adducts produced.

g. Determined by HPLC.

h. Sonicated for 4 h, starting at 23 °C.

i. 2:1 Ether/hexanes.

j. 1,4-dioxane.

k. 1:1 THF/hexanes.

l. Confirmed by ^{1}H NMR. The same ratio was determined for ketones **7**, obtained by hydrolysis of adducts **15**.

It is apparent from the data for MeMgBr in ether (entries 1–5) that high diastereoselectivity in favor of the *R*-isomer is generally achieved with good yields of adducts **4** (80–95%), along with a small amount (3–11%) of unreacted aldehyde **6**. The best *R* selectivity is an impressive 98:2 (entry 1), which was obtained at the lowest temperature of −78°C. We observed just a moderate influence of temperature on the *R*:*S* ratio, which gradually decreased from 98:2 to 91:9 as the temperature increased from −78 to 35°C. At 0°C, the use of 5 mol equiv. of MeMgBr instead of 2 mol equiv., or 1:1 THF:ether instead of ether, exerted little effect on the *R*:*S* ratio (cf. entries 6 and 8 with entry 3).

Results for the reaction of EtMgBr and **6** in ether (entries 10–14) were very similar to those obtained with MeMgBr (entries 1–5). From −78 to 35°C, the yield of adducts **5** ranged from 75 to 90% and the *R*:*S* ratio gradually changed from 98:2 to 89:11. One difference in this case was the formation of reduced product **10**, the yield of which ranged from 7–11% with high yields occurring at higher temperatures. The formation of **10** was more accentuated in the reaction of *i*-PrMgBr and **6** in ether, with yields ranging from 31–47% (entries 15–19). This reductive side reaction with Grignard reagents is more prevalent for sterically hindered carbonyl substrates and bulkier organomagnesium reagents, such as those bearing secondary alkyl groups.[9] Thus, in the reaction of *i*-PrMgBr with **6** the yield of adducts **11** was only ca. 45–50%.[10] At −78°C, the *R*:*S* ratio of 98:2 for *i*-PrMgBr addition (entry 15) was identical to those for MeMgBr and EtMgBr addition. However, the *R*:*S* ratios at higher temperatures receded somewhat: e.g., at −20°C, 93:7 for *i*-PrMgBr (entry 16) vs. 97:3 for MeMgBr (entry 2); at 35°C, 86:14 for *i*-PrMgBr (entry 19) vs. 91:9 for MeMgBr (entry 5).

The reaction of $PhCH_2MgCl$ with **6** proved to be problematic in that the major product turned out to be an isomeric mixture of *o*-tolyl adducts **13**, rather than benzyl adducts **12** (entries 20 and 21). At 35°C, we obtained a 69% yield of **13** with an *R*:*S* ratio of 63:37. Although it is well known that allylic Grignard reagents add to carbonyl compounds with structural 1,3-rearrangement of the allylic group,[9b] this is a much less documented event with benzylic Grignard reagents.[11] There was too little benzyl adduct **12** formed to permit isolation of this material.

The addition of PhMgBr to **6** in ether proceeded smoothly, with yields of adducts **14** ranging from 80–97% and unreacted **6** ranging from 1–8% (entries 22–26). The *R*:*S* ratio decreased incrementally from 89:11 at −78°C to 76:24 at 35°C. For PhMgBr, the solvent had a strong impact on the *R*:*S* ratio, with THF and toluene at −78°C giving 64:36 (entry 27) and 46:54 (entry 28), respectively, relative to 89:11 for ether (entry 22).

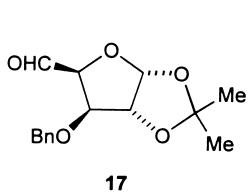
Addition of MeLi to **6** in ether at −78°C afforded an *R*:*S* ratio of 89:11 (entry 29), which falls significantly short of the 98:2 ratio attained with MeMgBr (entry 2). By the same token, the *R*:*S* ratio of 80:20 for PhLi addition to **6** in ether at −78°C (entry 30) was lower than the 89:11 ratio attained with PhMgBr (entry 22). Bulky *t*-BuLi gave only a 30% yield of adduct, with a ratio of 87:13 (entry 31). Two other lithium reagents, $LiCH_2CO_2$-*t*-Bu and 2-lithio-2-ethyl-1,3-dithiane, were also studied because of the above-mentioned reports of Izquierdo et al.[7] and Heathcock et al.,[4] respectively. The addition of $LiCH_2CO_2$-*t*-Bu to **6** in ether:hexanes (2:1) at −78°C furnished adducts **9** in 87% yield with an *R*:*S* ratio of 80:20 (entry 32). The related Reformatsky reaction of **6** with $BrCH_2CO_2Me$ and zinc was conducted under sonication conditions in 1,4-dioxane, starting at 23°C but with the temperature being elevated over time, to afford **8** in 80% yield with an improved *R*:*S* ratio of 90:10 (entry 33). Reaction of 2-lithio-2-ethyl-1,3-dithiane with **6** in THF:hexanes (1:1) at −70°C, followed by warming to 23°C, gave a 63% yield of adducts **15** (EDT=2-ethyl-1,3-dithian-2-yl) with an excellent *R*:*S* ratio of 94:6 (entry 34). One might be tempted to attribute this 94:6 stereoselectivity to the bulkiness of the nucleophile; however, the 87:13 ratio of **16a**:**16b** obtained with *t*-BuLi would suggest otherwise. Perhaps this very favorable result for the dithiane addition is connected with stabilization of the nucleophile or a reagent aggregation phenomenon.

Our results when adding the lithio dithiane to **6** are fairly consistent with the results of Heathcock et al.,[4] although they did not report the formation of the minor diastereomer, **15b**, or its hydrolysis product, **7b**. Similarly, our results when adding $LiCH_2CO_2$-*t*-Bu and $BrZnCH_2CO_2Me$ to **6** are consistent with those reported by Izquierdo et al.[7] However, our experience when adding MeMgBr to **6** is not in agreement with the results described by Martinez et al.[6] At 20°C, we obtained an *R*:*S* ratio of 91:9, rather than a single isomer (**4a**); also, we obtained an *R*:*S* ratio of ca. 90:10 at 35°C, rather than a 60:40 mixture of **4a** and **4b**. Since our Grignard reagent was different (MeMgBr vs. MeMgI), we decided to react **6**

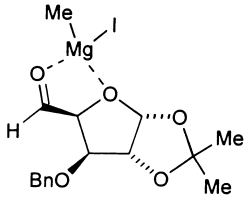
with MeMgI in ether at 35°C. The *R*:*S* ratio turned out to be 89:11 (91% yield), virtually the same as for MeMgBr addition.

2.2. Stereochemistry of addition

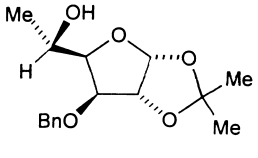
Addition of carbanion reagents, such as Grignard reagents, to sugar aldehydes has been noted to occur with high diastereoselectivity in various cases.[12] However, current models of asymmetric induction that are useful for predicting the direction, and even degree, of stereochemical bias for the addition of nucleophiles to α-chiral aldehydes may not be suitable for carbohydrate systems.[12d,13] A cyclic chelate model was originated by Wolfram and Hanessian to explain the high diastereoselectivity of addition of carbanion reagents to furanose aldehyde **17**.[12a] For the addition of MeMgI in THF:ether, they suggested formation of a five-membered ring bidentate chelate, involving the aldehyde and furanose ring oxygen atoms (viz. **18**), which would then be attacked preferentially from the less hindered α face of the carbonyl group to furnish mainly **19**.



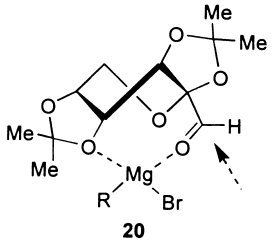
17



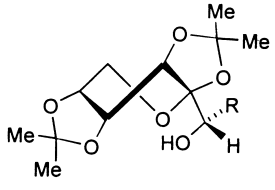
18



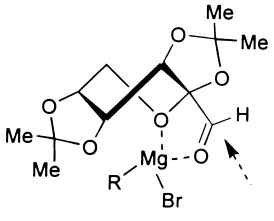
19



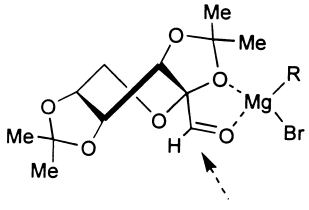
20



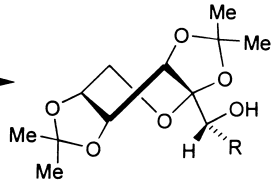
23 (minor)



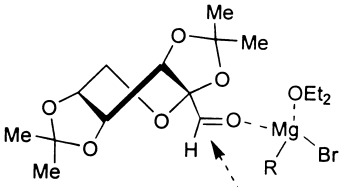
21



22



24 (major)



25

For aldehyde **6**, in a skew $^3S_0$ conformation, oxygen atoms O1, O2, O4, and O6 are available for bidentate chelation to Mg^{2+}, to provide cyclic complexes **20**, **21**, or **22**. Approach of the Grignard reagent is disfavored from the β face of the aldehyde in these three structures due to the steric hindrance imposed by H3 and the proximal methyl group of the 2,3-ketal. Hence, attack from the α face would be strongly

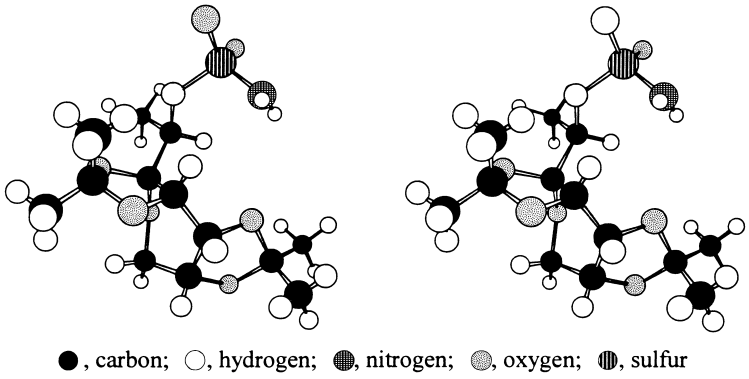


Figure 1. Stereoview of a ball and stick model of the X-ray crystal structure of **2a**

preferred. A seven-membered ring chelate **20** is considered, despite its being structurally challenged, since an intramolecular hydrogen bond between the C1 hydroxyl and O4 in diacetone fructose (**10**) has been noted.[3a,14a] If chelates **20** and **21** were predominant, then attack from the α face would favor formation of **23**, which is the minor *S*-diastereomer. On the other hand, chelate **22**, a five-membered ring complex involving O1 and O2, is the only bidentate chelate that would favor formation of **24**, which is the major *R*-diastereomer. In support of chelate **22**, we observed a significant decrease in diastereoselectivity (98:2 to 89:11) with MeLi compared to MeMgBr (cf. entries 29 and 1 in Table 1). A similar decrease in diastereoselectivity (95:5 to 72:27) was found[12b] in the reactions of phenylsulfonylmethides with **17** after changing the counterion from Mg^{2+} to Li^{+}, and Kim et al.[12b] attributed the decrease to the stronger β-chelating ability of Mg^{2+} relative to Li^{+}. Major diastereomer **24** could also be produced by a Felkin–Anh transition state[17] instead of cyclic chelate **22**. A likely structure for the Felkin–Anh pathway would have O6 antiperiplanar to the aldehyde oxygen, as depicted in **25**. In the other possible Felkin–Anh structure, with O2 antiperiplanar to the aldehyde oxygen, attack from the aldehyde β face would result in the formation of the minor diastereomer, **23**.

*2.3. X-Ray crystal structure of **2a***

A single crystal of **2a** was subjected to an X-ray diffraction study, which established the *R* stereochemistry at the carbinol carbon (C1). It is apparent that the pyran ring of **2a** adopts a skew conformation ($^3S_0$) in the solid state (Fig. 1). This conformation is the one adopted by such tricyclic sugars, as with topiramate (**1**) and related compounds, in the solid state and in solution, presumably because of the '*cis–anti–cis*' arrangement for the 5–6–5 tricyclic ring system.[1a,3a,14–16]

2.4. NMR studies of the adducts

There are no spectroscopic criteria available to assign *R*:*S* configuration to the products of carbanion addition to **6**. Although the recent paper by Izquierdo et al.[7] discloses ^{1}H NMR data for the isomers of **8** and **9**, the information provided is not sufficient to offer a method for making stereochemical assignments. Thus, we have collected ^{1}H and ^{13}C NMR data for several pairs of *R*- and *S*-isomers (Tables 2–7) to identify trends in the spectral parameters that would be useful for making such predictions.

It is worth noting initially that the values for the ^{1}H NMR coupling constants $J_{3,4}$, $J_{4,5}$, $J_{5,6e}$, and $J_{5,6a}$ (Tables 4 and 5) indicate a skew conformation ($^3S_0$), as the corresponding coupling constants for topiramate (**1**) are 2.6, 8.0, 1.9, and 0.8 Hz. Inspection of the proton chemical shifts and coupling

Table 2
^{1}H NMR chemical shifts (ppm) for major isomers

cmpd	H1	H3	H4	H5	H6	H6'	OH/NH_2	R
2a	4.68 q	4.45 d	4.64 dd	4.27 dd	3.82 d	3.94 dd	4.97 br s	1.59 d
4a	3.81 m	4.47 d	4.61 dd	4.25 dd	3.80 d	3.94 dd	1.82 br s	1.33 d
5a	3.52 m	4.49 d	4.61 dd	4.24 dd	3.78 d	3.93 dd	1.72 d	1.35 t, 1.99 m
7a	4.28 d	4.65 d	4.67 dd	4.26 dd	3.78 d	3.91 dd	3.89 d	1.12 t, 2.59 m, 3.00 m
8a	4.10 m	4.60 d	4.62 dd	4.24 dd	3.76 dd	3.90 dd	3.12 d	2.64 dd, 2.92 dd, 3.71 s
9a	4.04 m	4.61 s	4.63 dd	4.25 dd	3.75 d	3.91 dd	3.30 d	2.52 dd (CH_2), 2.82 dd
11a	3.56 dd	4.46 d	4.63 dd	4.24 dd	3.77 d	3.93 dd	1.67 d	0.93 d, 1.01 d, 2.35 m
13a	5.18 d	4.64[a]	4.67[a]	4.26 dd	3.82 d	3.95 dd	2.95 d	2.44 s, 7.13-7.65 m (4H)
14a	4.87 d	4.53 d	4.64 dd	4.27 dd	3.82 d	3.96 dd	3.05 d	7.28-7.50 m (5H)

a. Not possible to determine due to overlap of signals.

Table 3
^{1}H NMR chemical shifts (ppm) for minor isomers

cmpd	H1	H3	H4	H5	H6	H6'	OH/NH_2	R
2b	4.72 q	4.47 d	4.58 dd	4.28 dd	3.90 d	3.92 dd	4.87 br s	1.58 d
4b	3.79 m	4.35 d	4.60 dd	4.26 dd	3.82 d	3.91 dd	2.87 d	1.32 d
5b	3.45 m	4.35 d	4.58 dd	4.25 dd	3.80 d	3.89 dd	2.74 d	1.05 t, 1.57-1.75 m
7b	4.12 d	4.46 d	4.49 dd	4.13 dd	3.65 d	3.74 dd	3.66 d	1.01 t, 2.53 m, 2.83 m
8b	4.13 m	4.41 d	4.60 dd	4.24 dd	3.79 d	3.87 dd	3.19 d	2.64 dd, 2.74 dd, 3.72 s
9b	4.08 m	4.40 d	4.58 dd	4.23 dd	3.78 d	3.87 dd	3.11 d	1.47 s, 2.55 dd, 2.71 dd
11b	3.28 dd	4.41 d	4.60 dd	4.24 dd	3.76 d	3.86 dd	2.87 d	1.03 d, 1.05 d, 2.14 m
13b	5.06 d	4.43 d	4.68 dd	4.29 dd	3.82 d	3.90 dd	3.87 d	2.45 s, 7.12-7.69 m (4H)
14b	4.78 d	4.44 d	4.67 dd	4.27 dd	3.79 d	3.88 dd	3.80 d	7.28-7.52 m (5H)

constants for the major (**a**) and minor (**b**) isomeric series (Tables 2–5) does not reveal any parameter suitable for assigning stereochemistry at C1.

Many of the carbon chemical shifts (Tables 6 and 7) are also uninformative with respect to assigning stereochemistry; however, the chemical shifts for C1 and C3 appear to be nicely diagnostic. For eight isomeric pairs, the δC1 values for the major isomer (*R* series on the basis of the assignment for **4a** via **2a**) are significantly upfield, by ca. 2–4 ppm, relative to the δC1 values for the minor isomer (*S* series). Furthermore, the δC3 values for the major isomer (*R* series) are significantly upfield, by ca. 2.5 ppm, relative to the δC3 values for the minor isomer (*S* series). This latter parameter is quite impressive in that the difference between the δC3 values for the isomeric pairs is so constant, basically 2.5±0.1, over eight

Table 4
^{1}H NMR coupling constants (Hz) for major isomers

cmpd	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{6a,6e}$	$J_{1,OH}$	$J_{1,\alpha}$
2a	2.35	7.83	1.86	12.91	- -	7.26
4a	2.74	7.83	1.90	12.91	*a*	6.5
5a	2.35	7.83	1.89	13.30	5.6	*b*
7a	2.82	7.63	1.91	12.90	7.45	- -
8a	2.35	7.83	1.86	12.91	6.65	3.13, 16.4
9a	*b*	7.83	1.76	13.30	6.65	3.13
11a	2.74	7.83	1.79	12.91	11.35	2.35
13a	*b*	7.43	1.96	12.91	4.70	- -
14a	2.74	7.83	1.88	13.30	5.09	- -

a. Not observed.

b. Not possible to determine due to the non-first-order pattern.

Table 5
^{1}H NMR coupling constants (Hz) for minor isomers

cmpd	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{6a,6e}$	$J_{1,OH}$	$J_{1,\alpha}$
2b	2.16	8.39	1.62	12.99	- -	6.49
4b	2.35	7.83	1.99	12.91	3.91	6.45
5b	2.35	7.83	2.01	13.30	4.70	- -
7b	2.34	7.86	2.12	13.22	6.83	- -
8b	2.35	7.83	1.96	13.30	4.30	16.04, 3.13
9b	2.35	7.83	1.93	13.30	4.30	3.13, 9.34
11b	2.35	7.83	1.96	12.91	6.26	5.10
13b	2.74	7.83	1.96	12.91	3.13	- -
14b	2.74	7.83	1.95	13.30	3.13	- -

adducts. Although only **4a** is firmly established as having the *R* configuration at C1 by X-ray analysis of **2a**, we suggest that the trend observed in ^{13}C NMR chemical shifts for C1 and C3 may offer a useful diagnostic for the assignment of *R*:*S* configuration for the carbanion adducts of **6**.

The X-ray crystal structure of **2a** (Fig. 1) displays a staggered conformation about the C1–C2 bond in which the methyl group is directed between O2 and O6, while H1 is directed between O6 and C3. This is a reasonable candidate for the most stable of the three staggered conformations for C1–C2 in solution because the larger groups would impinge on the *endo* (more proximal) methyl group on the 4,5-ketal in the two other conformers and the bulkier methyl group is favorably disposed between two ether oxygen atoms. For the corresponding *S*-isomer, **2b**, while maintaining this favorable arrangement, the

Table 6
^{13}C NMR chemical shifts (ppm) for major isomers

cmpd	C1	C2	C3	C4	C2'/C4'	C5	C6	R
2a	80.79	102.94	70.31	70.52	109.60/109.30	70.88	61.50	15.58
4a	69.96	104.94	70.57	70.70	108.69/109.34	71.20	61.70	17.89
5a	75.31	104.94	70.72	70.84	108.73/109.35	71.23	61.67	11.06, 24.41
7a	76.63	104.05	70.74	70.79	109.66/109.47	71.22	62.06	7.99, 35.19, 205.50
8a	71.18	103.97	70.17	70.66	109.37/109.05	70.04	61.66	35.96, 52.17, 174.08
9a	70.17	104.07	70.09	70.69	108.94/109.32	71.22	61.56	37.04
11a	76.39	104.76	71.61	70.76	109.05/109.40	71.28	61.75	15.97, 21.82, 27.71
13a	71.35	105.76	70.51	70.51	109.32/109.42	71.13	61.79	20.62, 126.0/128.0/128.1/ 130.5/138.1/138.2
14a	75.84	104.86	70.55	70.52	109.51/109.62	71.27	61.95	128.2/128.4/129.0/139.4

Table 7
^{13}C NMR chemical shifts (ppm) for minor isomers

cmpd	C1	C2	C3	C4	C2'/C4'	C5	C6	R
4b	72.11	104.95	73.05	70.37	108.68/109.57	71.09	61.36	16.92
5b	77.66	105.19	73.17	70.40	108.49/108.57	71.03	61.28	11.22, 24.14
7b	80.65	104.29	72.23	70.52	109.50/109.28	70.58	61.54	7.79, 26.71
8b	72.64	104.35	72.84	70.24	109.62/109.02	70.92	61.36	36.89, 52.12, 173.15
9b	72.63	104.59	72.57	70.33	109.49/108.79	70.90	61.25	28.50, 38.20, 80.87, 172.14
11b	81.02	105.84	74.16	70.62	109.64/108.75	71.10	61.20	18.56, 29.82
13b	74.10	105.06	73.00	70.47	109.56/109.97	71.37	61.81	20.69, 125.7/128.2/130.4/ 130.5/136.6/136.8
14b	78.53	104.24	72.90	70.52	109.42/109.91	71.25	61.85	128.0/128.3/129.1/138.6

methyl group and O1 would be interchanged, resulting in a somewhat less favorable steric positioning of the methyl group vis-à-vis O2 and C3. In the case of the related alcohols, the hydroxyl group on C1 is probably involved in intramolecular hydrogen bonding with O4, as in diacetone fructose (**10**),[3a,14a] whereas this interaction does not occur in the corresponding sulfamates.[3a] Thus, in the *R*-isomer the methyl group would be oriented between O2 and C3 and in the *S*-isomer the methyl group would be oriented between O2 and O6, which is a less sterically demanding situation. This arrangement for the *R*-isomer would place C3 in a particularly crowded environment. Given such a steric picture, it is reasonable to think that the ^{13}C NMR chemical shift differences at C2 and C3 — significant shielding for the *R*-isomer relative to the *S*-isomer — is a consequence of standard ^{13}C NMR steric shielding effects.[18]

3. Conclusion

The addition of various carbanionic reagents to 'diacetone fructose aldehyde' (**6**) can afford a high level of stereocontrol at C1 (≥80%). The reagents MeMgBr, EtMgBr, *i*-PrMgBr, MeMgI, and 2-lithio-2-ethyl-1,3-dithiane resulted in a high bias (≥90%) for one diastereomer, assigned as the *R*-isomer. The reaction of PhMgBr showed lower diastereoselectivity and a significant dependence of the isomer ratio on temperature and solvent. Contrary to an earlier report,[6] methyl Grignard reagents were found not to show a pronounced temperature dependence for the isomer ratio. The *R* absolute stereochemistry at the carbinol C1 center of **4a** was established through X-ray analysis of sulfamate derivative **2a**. Carbon-13 NMR chemical shift data, specifically the trends in chemical shifts for C1 and C3, were identified as a tool for assigning stereochemistry to the C1 adducts of **6**.

4. Experimental

4.1. General methods

The X-ray crystallography work on **2a** was conducted by Crystalytics Co., Lincoln, NE. TLC separations were conducted on Whatman MK6F silica gel 60A plates (250 μm) with visualization by iodine staining and by charring with EtOH:H_2SO_4 (95:5). Column chromatography was performed on silica gel 60 (40–63 mm; EM Science). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at the sodium D line (λ=589 nm). NMR spectra were acquired as described below (s, singlet; d, doublet; t, triplet; m, multiplet; br, broad). GLC was performed on a Hewlett Packard 5890 Series II capillary gas chromatograph equipped with a Chrompack CPSil 5CB capillary column (25 m×0.25 mm I.D.×0.12 μm film thickness) and flame-ionization detector with helium as the carrier gas with a flow rate of 30 cm/s at 185°C. The injection port and detector temperatures were 280 and 300°C, respectively. GLC analysis conditions used: 120–140°C at 2°C/min for **4** and **16**; 120°C for **5**; 120–180°C at 7°C/min for **8**, **9**, and **14**; 120–180°C at 5°C/min for **7**; 120–200°C at 10°C/min for **15**; 140°C for **11**; 150–180°C at 2°C/min for **13**. HPLC analysis was performed on a Hewlett–Packard Series 1100 high-performance liquid chromatograph, eluting isocratically with water:acetonitrile:trifluoroacetic acid (350:150:1) at 0.75 mL/min on a Supelcosil ABZ+plus column (5 cm×2.1 mm; 3 μm particle size) at 40°C and recording signals simultaneously at 220 nm and 254 nm with a diode array detector. GC–MS samples were analyzed on a Hewlett–Packard 5890 gas chromatograph equipped with a HP-1 capillary column (12 m×0.2 mm I.D.×0.33 μm film thickness) interfaced to a Hewlett–Packard 5970 mass-selective detector, with helium as the carrier gas. The injector and transfer line of the instrument were held at 280°C and the column temperature was increased from 80–280°C at 10°C/min. The ionization method used was electron impact (70 eV) and the mass spectrometer was scanned from 40–800 amu at 425 amu/s. Compounds **4**–**16** were generally identified by a diagnostic $(M-15)^+$ peak, which corresponds to loss of a methyl group; no parent ions were ever observed. Chemical ionization mass spectra were obtained on a Hewlett–Packard 5989A instrument using ammonia (source pressure=1 torr). Samples were introduced by a Hewlett–Packard 1050 LC system coupled to a Hewlett–Packard 59980B particle beam interface. The mass spectrometer was scanned from 110–1000 amu at a rate of 712 amu/s. Accurate mass determinations were performed on an Autospec E high resolution magnetic sector mass spectrometer tuned to a resolution of 6 K. The ions were produced in a fast-atom bombardment source at an accelerating voltage of 8 kV. Linear voltage scans at 33 amu/s were collected to include the sample ion and two polyethylene glycol ions, which were used as internal reference standards.

4.2. Procedures for reaction of aldehyde **6** with organometallic reagents

To a solution of aldehyde **6** (260 mg, 1 mmol) in 10 mL of dry solvent under argon was added the organometallic reagent (2 mmol) at the given temperature (Table 1). The reaction mixture was stirred at the same temperature for 2 h, at which time the reaction was quenched with 10 mL of 10% ammonium chloride. The organic layer was separated and the aqueous phase was extracted twice with 5 mL of ethyl acetate. The combined extracts were washed with saturated sodium chloride, dried (Na_2SO_4), and concentrated to give the crude product, which was analyzed by GLC, GLC–MS, and ^{1}H NMR.

The reactions of **6** with methyl bromoacetate, lithio *tert*-butylacetate, and 2-lithio-2-ethyl-1,3-dithiane were conducted exactly as described in literature.[4,7]

4.3. 1-Deoxy-3,4:5,6-bis-O-(1-methylethylidene)-β-D-gluco-3-heptulopyranose sulfamate (**2b**)

Alcohol **4b** (2.2 mg, 0.008 mmol) was reacted with sodium hydride (0.4 mg, 0.016 mmol) and sulfamoyl chloride (1.9 mg, 0.016 mmol) in DMF (0.5 mL) as described for compound **2a**.[3a] The crude product was triturated three times with hexanes and dried in vacuo to afford crude **2b** (2.8 mg, 100%). CI/MS *m*/*z* 354 $(MH)^+$, 371 $(M+NH_4^+)$; HR/MS calcd for $C_{13}H_{23}NO_8S$ $(M+NH_4^+)$ 371.1483, found 371.1488.

4.4. General methods for the isolation of stereoisomerically enriched alcohols

To obtain both isomers pure, the crude product mixtures with the poorest stereoselectivity were subjected to column chromatography on silica gel with CH_2Cl_2:hexane:acetone (25:5:1) for **4** and **5**; hexane:ethyl acetate (4:1) for **7**, **13**, and **14**; hexane:ethyl acetate (5:1) for **8** and **9**; and toluene:acetone (15:1) for **11**. In most cases, we obtained each isomer stereochemically pure as colorless sticky syrups or white crystals; however, in the case of the minor isomers of ester **8** and ketone **7** we obtained only enriched mixtures in a ratio of 75:25 in favor of minor isomer. The diastereomers of compound **16** were not separated [^{1}H NMR (**16a**) δ 1.06 (s, 9H, *t*-Bu), 1.35, 1.44, 1.50, 1.55 (4s, 3H, Me), 1.81 (d, 1H, OH), 3.40 (d, 1H, H1, $J_{1,OH}$=11.35 Hz), 3.75 (d, 1H, H6e), 3.90 (dd, 1H, H6a, $J_{6a,6e}$=12.91 Hz), 4.21 (dd, 1H, H5, $J_{4,5}$=7.83 Hz, $J_{5,6a}$=1.96 Hz), 4.51 (d, 1H, H3), 4.62 (dd, 1H, H4, $J_{3,4}$=2.74 Hz). ^{13}C NMR (**16a**) δ 24.32, 27.38, 28.19, 36.28, 61.51, 70.74, 71.07, 72.27, 78.44, 106.59, 109.16, 109.32]. HR/MS calcd for $C_{13}H_{22}O_6$ $(MH)^+$ 317.1937, found 317.1942.

4.5. Stereoisomerically enriched alcohols

4a: Yield of pure isomer after chromatography was 77%; $[\alpha]_D^{25}$ −23.7 (*c* 0.7, $CHCl_3$). CI/MS *m*/*z* 275 $(MH)^+$, 292 $(M+NH_4^+)$; HR/MS calcd for $C_{13}H_{22}O_6$ $(MH)^+$ 275.1495, found 275.1487.

4b: Yield of pure isomer after chromatography was 6%; $[\alpha]_D^{25}$ −8.8 (*c* 0.3, $CHCl_3$). HR/MS calcd for $C_{13}H_{22}O_6$ $(MH)^+$ 275.1495, found 275.1492.

5a: Yield of pure isomer after chromatography was 47%; $[\alpha]_D^{25}$ −13.9 (*c* 0.8, $CHCl_3$). CI/MS *m*/*z* 289 $(MH)^+$, 306 $(M+NH_4)^+$; HR/MS calcd for $C_{14}H_{24}O_6$ $(MH)^+$ 289.1651, found 289.1651.

5b: Yield of pure isomer after chromatography was 4%; $[\alpha]_D^{25}$ −18.5 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 289 $(MH)^+$, 306 $(M+NH_4)^+$; HR/MS calcd for $C_{14}H_{24}O_6$ $(MH)^+$ 289.1651, found 289.1655.

7a: Yield of pure isomer after chromatography was 31%; $[\alpha]_D^{25}$ +55.0 (*c* 1.0, $CHCl_3$). CI/MS 316 *m*/*z* $(MH)^+$, 334 $(M+NH_4)^+$; HR/MS calcd for $C_{15}H_{24}O_7$ $(M-H)^+$ 315.1444, found 315.1438.

8a: Yield of pure isomer after chromatography was 48%; $[\alpha]_D^{25}$ −4.0 (*c* 1.0, $CHCl_3$). HR/MS calcd for $C_{15}H_{24}O_8$ $(M-H)^+$ 331.1393, found 331.1399.

9a: Yield of pure isomer after chromatography was 40%; $[\alpha]_D^{25}$ −4.0 (*c* 0.7, $CHCl_3$). CI/MS *m*/*z* 375 $(MH)^+$; HR/MS calcd for $C_{18}H_{30}O_8$ $(MH)^+$ 375.2019, found 375.2005.

9b: Yield of pure isomer after chromatography was 13%; $[\alpha]_D^{25}$ −14.5 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 375 $(MH)^+$; HR/MS calcd for $C_{18}H_{30}O_8$ $(MH)^+$ 375.2019, found 375.2014.

11a: Yield of pure isomer after chromatography was 23%; $[\alpha]_D^{25}$ −23.6 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 303 $(MH)^+$, 320 $(M+NH_4)^+$; HR/MS calcd for $C_{15}H_{26}O_6$ $(MH)^+$ 301.1651, found 301.1639.

11b: Yield of pure isomer after chromatography was 3%; CI/MS *m*/*z* 303 $(MH)^+$, 320 $(M+NH_4)^+$; HR/MS calcd for $C_{15}H_{26}O_6$ $(M-H)^+$ 301.1651, found 301.1642.

13a: Yield of pure isomer after chromatography was 17%; $[\alpha]_D^{25}$ −45.8 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 350 $(MH)^+$, 368 $(M+NH_4)^+$; HR/MS calcd for $C_{19}H_{26}O_6$ $(M-Me)^+$ 335.1495, found 335.1495.

13b: Yield of pure isomer after chromatography was 13%; $[\alpha]_D^{25}$ +20.4 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 350 $(MH)^+$, 368 $(M+NH_4)^+$; HR/MS calcd for $C_{19}H_{26}O_6$ $(MH)^+$ 349.1651, found 349.1652.

14a: Yield of pure isomer after chromatography was 40%; $[\alpha]_D^{25}$ −25.3 (*c* 0.8, $CHCl_3$). CI/MS *m*/*z* 337 $(MH)^+$, 354 $(M+NH_4)^+$; HR/MS calcd for $C_{18}H_{24}O_6$ $(M-Me)^+$ 321.1338, found 321.1335.

14b: Yield of pure isomer after chromatography was 16%; $[\alpha]_D^{25}$ +3.1 (*c* 1.0, $CHCl_3$). CI/MS *m*/*z* 337 $(MH)^+$, 354 $(M+NH_4)^+$; HR/MS calcd for $C_{18}H_{24}O_6$ $(M-Me)^+$ 321.1338, found 321.1341.

4.6. ^1H and ^{13}C NMR studies

All ^1H and ^{13}C 1D and 2D NMR spectra were recorded on a Bruker DMX-400 spectrometer at 298°K using a 5 mm multinuclear inverse *Z*-gradient probe. Samples were dissolved in $CDCl_3$ at concentrations ranging from 6–40 mg to 0.8 mL. Chemical shifts were measured relative to the solvent peak at 7.28 ppm for ^1H and 77.4 ppm for ^{13}C. Carbon multiplicities were assigned by distortionless enhancement by polarization-transfer experiments (DEPT). One-dimensional ^1H NMR spectra were collected with 32 K complex points and sweep widths ranging from 2400–6400 Hz, as needed. One-dimensional ^{13}C NMR (100.61 MHz) and DEPT spectra were collected with 64 K complex points and a sweep width of 22 kHz. Mild apodization functions were applied during data processing. Compounds **15a** and **15b** were additionally recorded in methanol-d_4 and at 600.13 MHz for resolution enhancement of pertinent peaks. These NMR spectra were recorded on a Bruker DMX-600 spectrometer equipped with an inverse 5 mm triple resonance probe (^1H:^{13}C:^{15}N) and triple axis gradients at 298 K. Two-dimensional gradient enhanced ^1H:^1H COSY and ^1H:^{13}C HETCOR experiments were conducted for some compounds to assist in making peak assignments. Two-dimensional COSY spectra were acquired in the magnitude mode with 1024 complex points collected in t_2 and 128 t_1 increments of 128 transients each. Two-dimensional HETCOR spectra were acquired in the magnitude mode with 2048 complex points collected in t_2 and 256 t_1 increments of 128 transients each. Two-dimensional data sets were processed using Bruker software. Matrix files were 1024×512 points in size for the COSY experiments and 2048×512 points in size for the HETCOR experiments. The t_2 and t_1 time domain transforms were weighted with a sine-shaped function shifted by 0° for both cases.

*4.7. X-Ray crystallography of **2a**[19]*

Single crystals of **2a**[3a] ($C_{13}H_{23}NO_8S$, mw 353.4, colorless rectangular parallelpipeds from ethanol:water; mp 152–153°C) are orthorhombic (space group $P2_12_12_1$ with a=7.9726(5) Å, b=14.395(1) Å, c=14.912(1) Å, α=β=γ=90.0°, V=1711.4(2) Å^3, and d_{calcd}=1.372 g cm^{-3} for Z=4. The intensity

data [a total of 2241 independent reflections having $2\theta(\text{MoK}\alpha)<54.98°$] were collected from a single crystal on a computer-controlled Siemens/Bruker P4 Autodiffractometer by using full ω scans at 293 K and graphite-monochromated MoKα radiation (λ=0.71073 Å). The Siemens/Bruker SHELXTL-PC software package was used to solve the structure by using the direct methods technique. All stages of weighted full-matrix least-squares refinement were performed with F_o^2 data and SHELXTL-PC Version 5 to converge at R_1 (unweighted, based on F)=0.053 for 1593 independent reflections having $2\theta(\text{MoK}\alpha)<54.98°$ and $I>2\sigma(I)$, and wR_2 (weighted, based on F^2)=0.127 for 2080 independent reflections having $2\theta(\text{MoK}\alpha)<54.98°$ and $I>0$. The structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. The sulfamate hydrogen atoms (H_{1N} and H_{2N}) were located from a difference Fourier map and refined as independent isotropic atoms. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms on their respective carbon atoms. The five methyl groups and their hydrogens were refined as rigid rotors with sp^3-hybridized geometry and a C–H bond length of 0.96 Å. The isotropic thermal parameters for H_{1N} and H_{2N} refined to final U_{iso} values of 0.08(2) and 0.09(3) Å^2. The remaining hydrogen atoms were included in the structure factor calculations fixed at 1.2 times (tertiary) and 1.5 times (methyl) the equivalent isotropic thermal parameter of the carbon to which they were bonded. The final refined value of 0.34(16) for the 'Flack' absolute structure parameter did not permit an assignment of the absolute configuration by use of the diffraction data alone.

Acknowledgements

We thank Samuel O. Nortey for some technical assistance.

References

1. (a) Maryanoff, B. E.; Nortey, S. O.; Gardocki, J. F.; Shank, R. P.; Dodgson, S. P. *J. Med. Chem.* **1987**, *30*, 880–887; (b) Shank, R. P.; Gardocki, J. F.; Vaught, J. L.; Davis, C. B.; Schupsky, J. J.; Raffa, R. B.; Dodgson, S. J.; Nortey, S. O.; Maryanoff, B. E. *Epilepsia* **1994**, *35*, 450–460; (c) Maryanoff, B. E.; Margul, B. L. *Drugs Future* **1989**, *14*, 342–344; (d) Follow-up reviews: Anon. *Ibid.* **1993**, *18*, 397–398; Anon. *Ibid.* **1994**, *19*, 425; Anon. *Ibid.* **1995**, *20*, 444–445; Anon. *Ibid.* **1997**, *22*, 458–460; (e) Perucca, E. *Pharmacol. Res.* **1997**, *35*, 241–256; (f) Ben-Menachem, E. *Expert Opin. Invest. Drugs* **1997**, *6*, 1085–1094; (g) Langtry, H. D.; Gillis, J.. C.; Davis, R. *Drugs* **1997**, *54*, 752–773; (h) Privitera, M. D. *Ann. Pharmacother.* **1997**, *31*, 1164–1173; (i) Sachdeo, R. C. *Clin. Pharmacol.* **1998**, *34*, 335–346.
2. (a) Kanda, T.; Kurokawa, M.; Tamura, S.; Nakamura, J.; Ishii, A.; Kuwana, Y.; Serikawa, T.; Yamada, J.; Ishihara, K.; Sasa, M. *Life Sci.* **1996**, *59*, 1607–1616; (b) White, H. S.; Brown, S. D.; Skeen, G. A.; Twyman, R. E. *Epilepsia* **1995**, *36* (*S4*), 34; (c) White, H. S.; Brown, S. D.; Woodhead, J. H.; Skeen, G. A.; Wolf, H. H. *Epilepsy Res.* **1997**, *28*, 167–179; (d) Severt, L.; Gibbs III, J. W.; Coulter, D. A.; Sombati, S.; DeLorenzo, R. J. *Epilepsia* **1995**, *36* (*S4*), 38; (e) Sombati, S.; Coulter, D. A.; DeLorenzo, R. J. *Epilepsia* **1995**, *36* (*S4*), 38; (f) Zona, C.; Ciotti, M.; Avioli, M. *Neurosci. Lett.* **1997**, *231*, 123–126.
3. (a) Maryanoff, B. E.; Costanzo, M. J.; Nortey, S. O.; Greco, M. N.; Shank, R. P.; Schupsky, J. J.; Ortegon, M. P.; Vaught, J. L. *J. Med. Chem.* **1998**, *41*, 1315–1343; (b) The samples of **2** and **3** examined for anti-convulsant activity were enriched in the *R*-isomer (**2a**/**3a**) and were virtually devoid of activity (see Ref. 3a) We did not have the opportunity to prepare and test samples enriched in the *S*-isomer (**2b**/**3b**).
4. Heathcock, C. H.; White, C. T.; Morrison, J. J.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296–1309.
5. In fact, a recent discussion (Heathcock, C. H., personal communication, 1997) confirmed that the configuration in question is not established by Ref. 4.
6. Martinez, E.; Gonzalez, A. N.; Echavarren, D. *An. Quim., Ser. C* **1980**, *76*, 230–232.
7. Izquierdo, I.; Plaza, M. T., Robles, R.; Mota, A. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2597–2606.
8. (a) Izquierdo et al. (see Ref. 7) also reported that **6** reacts with dimethylsulfonium methoxycarbonylmethylide (in THF:DMSO, 23°C → 60°C) to afford a single product, the (*R*)-epoxide; (b) The addition of cyanide to **6** was reported

(Kuszmann, J.; Marton-Meresz, M.; Jerkovich, G. *Carbohydr. Res.* **1988**, *175*, 249–264) to give an 85:15 ratio of cyanohydrins (ether:water, 23°C), but an assignment of stereochemistry was not made. Although this addition showed a strong stereochemical bias, it probably resulted from equilibrium control, rather than kinetic control.

9. (a) March, J. *Advanced Organic Chemistry*, 2nd edition; McGraw-Hill: New York, 1977, pp. 838–840; (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B*, 2nd edition; Plenum Press, New York, 1983, pp. 260–261.
10. The fairly constant yields for adducts **11** are a consequence of a balance between the amounts of reduction product **10** and unreacted aldehyde **6**.
11. (a) Bernardon, C.; Deberly, A. *J. Org. Chem.* **1982**, *47*, 463–468; (b) Bernardon, C. *J. Organometal. Chem.* **1989**, *367*, 11–17.
12. For example, see: (a) Wolfrom, W. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800–1804; (b) Kim, K. S.; Ahn, Y. H.; Park, S. B.; Cho, I. H.; Joo, Y. H.; Youn, B. H. *J. Carbohydr. Chem.* **1991**, *10*, 911–915; (c) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69–134; (d) Giuliano, R. M.; Villani, F. J., Jr. *J. Org. Chem.* **1995**, *60*, 202–211.
13. (a) Boyd Jr., F. L.; Baker, D. C. *J. Carbohydr. Chem.* **1986**, *5*, 257–269; (b) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819.
14. (a) Maeda, T.; Tori, K.; Saton, S.; Tokuyama, K. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2635–2647; (b) Brady Jr., R. F. *Adv. Carbohydr. Chem. Biochem.* **1971**, *26*, 197–278.
15. (a) Maryanoff, B. E.; Costanzo, M. J.; Shank, R. P.; Schupsky, J. J.; Ortegon, M. E.; Vaught, J. L. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2653–2656; (b) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009–5012.
16. It should be noted that the presentation of chair structures for such tricyclic sugars in references 6 and 7 is not consistent with the expected skew conformation (see Refs 14 and 15).
17. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199–2204.
18. Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; Wiley-Interscience: New York, 1972, pp. 43–44.
19. Tables of bond distances, bond angles, and positional and thermal parameters are available on request from the corresponding author.