201. Reactions of Chiral 2-(*tert*-Butyl)-2*H*,4*H*-1,3-dioxin-4-ones Bearing Functional Groups in the 6-Position and Diastereoselective Catalytic Hydrogenation to *cis*-2,6-Disubstituted 1,3-Dioxan-4-ones

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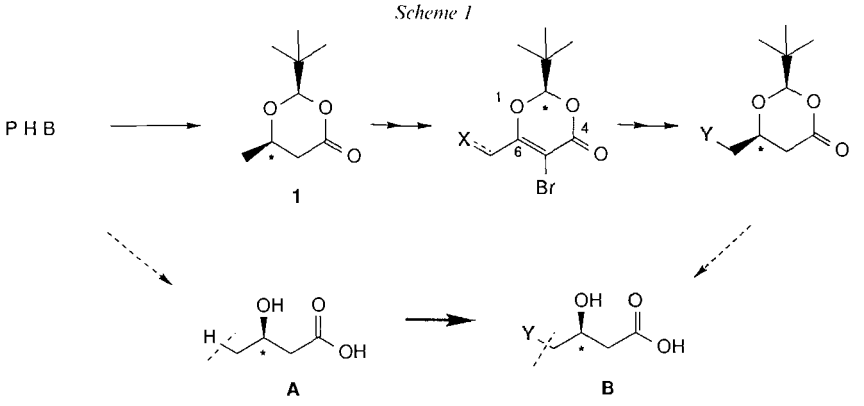
(22.IX.87)

(*R*)-5-Bromo-6-(bromomethyl)-2-(*tert*-butyl)-2*H*,4*H*-1,3-dioxin-4-one (**2**) derived from (*R*)-3-hydroxybutanoic acid is used for substitutions and chain elongations at the side-chain C-atom in the 6-position of the heterocycle (→**3–6**, **10–13**). Subsequent simultaneous reductive debromination and double-bond hydrogenation (Pd/C,H_2) occurs with essentially complete diastereoselectivity (> 98% ds), with H transfer from the face opposite to the *t*-Bu group (→**15–20**, *Table 1*). Hydrolytic cleavages of the dioxanones then lead to enantiomerically pure β-hydroxy-acid derivatives (overall self-reproduction of the stereogenic center of 3-hydroxybutanoic acid or alkylation in the 4-position of this acid with preservation of configuration).

In the course of our work on the use of the biopolymer polyhydroxybutyrate/valerate (PHB/PHV) [1], we have found that it is possible to prepare non-racemic dioxinones with a pivalaldehyde-derived stereogenic center, see *Scheme 1* [2] [3]. We describe here reactions of such dioxinones at the side chain in position 6 of the heterocyclic ring[2]), followed by diastereoselective catalytic hydrogenation with regeneration of a stereogenic center in that position. Thus, in the overall transformation, a hydrogen atom in the 4-position of

Scheme 1



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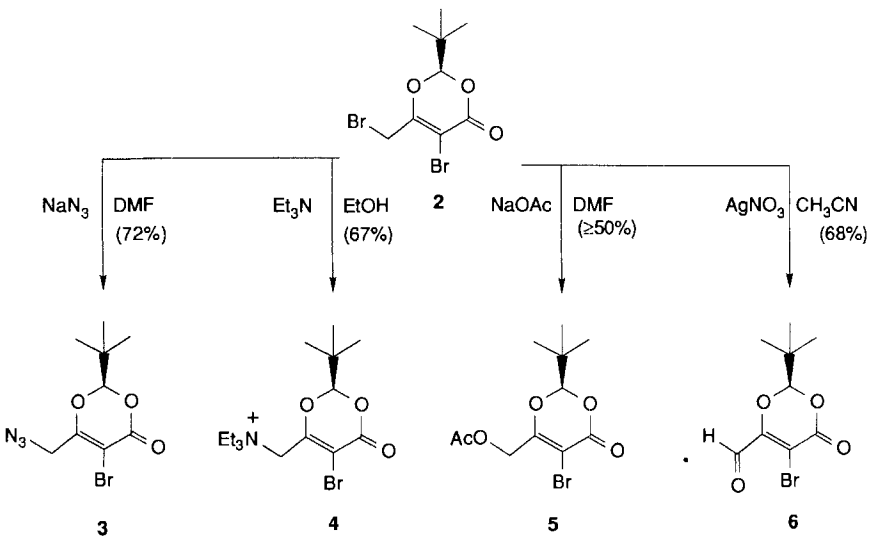
[2]) *Michael* additions to chiral dioxinones will be described in a separate paper.

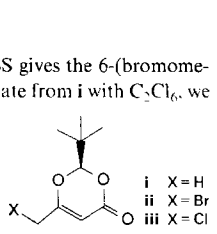
hydroxybutanoic acid is replaced – with preservation of the configuration at C(3), see **A**→**B** in *Scheme 1*.

The key intermediate for the reactions investigated is the dibromide **2** which can be obtained [3] directly from the dioxanone **1** in up to 50% yield by bromination with *N*-bromosuccinimide (NBS) (0.1-molar scale[3]), see details of optimization of this reaction in the *Exper. Part*). The allylic-bromide moiety of **2** can be reacted with different nucleophiles[4]) as shown in *Scheme 2*. The ammonium salt **4** and the acetate **5** were not used for further reactions and, therefore, were not fully characterized. The nicely crystalline azide **3** and especially the aldehyde **6** turned out to be useful intermediates for further transformations. $AgNO_3$ and the dibromide **2** gave the nitrate ester as a not isolated intermediate. We noticed that crude products were mixtures of the ester and the aldehyde (^{1}H-NMR analysis). If the reaction mixture was heated to reflux of MeCN before workup, only the aldehyde **6** was isolated. Normally, the nitrite elimination from nitrate esters to form carbonyl compounds requires base[5]).

Scheme 2



[3]) Bromination of the 2-(*tert*-butyl)-6-methyl-2*H*,4*H*-1,3-dioxin-4-one (**i**) [3] with NBS gives the 6-(bromomethyl)-2-(*tert*-butyl)-2*H*,4*H*-1,3-dioxin-4-one (**ii**; 34%). By chlorination of the dienolate from **i** with C_2Cl_6, we obtained the chloro analogue **iii** (55%). Such halogenations have been described for the achiral acetonide of acetoacetic acid enol in [4]. We tried *Wittig* reactions using the triphenylphosphonium salt from **ii** and **iii**, without much success. Olefinations of the aldehyde **6** by *Wittig* reagents turned out to be a more efficient reaction for chain elongation (see *Scheme 3* and the *Footnote* [4]).

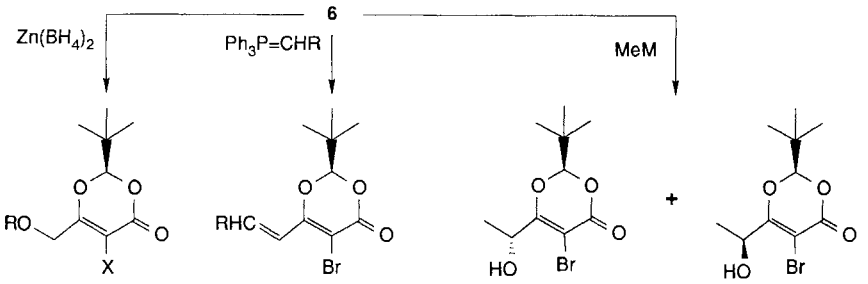


[4]) Nucleophiles other than those shown in *Scheme 2* did not react as cleanly. Thus, NaCN in HMPA or DMF and **2** gave a complex mixture. Also, triphenylphosphine and **2** led to a partially debrominated substitution product, and sodium diethyl phosphite or triethyl phosphite gave mixtures of products which were not identified.

[5]) See the classical investigations by *Cristol, Hodosan, Boher, Letzinger, Rapoport, Emmaus*, and *Cava* (ref. 125–133 in *Smith*'s monography on nitrogen compounds [5]).

The bromoaldehyde **6** was reduced first with zinc borohydride (→**7**, 77%; *Scheme 3*), and then debrominated by hydrogenolysis (Pd/C) to the hydroxymethyl derivative **8** (overreduction to the unstable saturated hydroxymethyl-dioxanone could not totally be avoided)[6]. The (*tert*-butyl)dimethylsilyl-protected hydroxy compound **9** readily undergoes *Michael* addition of cuprate[2])[7]. With *Wittig* reagents, the aldehyde can be used for chain elongations, see **10** and **11** (75 and 90%, respectively; *Scheme 3*). Finally, we have added several nucleophilic methylating reagents to the carbonyl group of **6**. Of the two readily separated (flash chromatography) diastereoisomeric alcohols **12** (*l*-configuration) and **13** (*u*-configuration), one is formed preferentially, depending on the organometallic compound used: with MeLi, the attack occurs preferentially from the *Re*-face of the aldehyde-carbonyl plane (→**12**), with MeZnCl[8]) from the *Si*-face (chemical correlation as structure proof, see below). This result is reminiscent of *Mukaiyama*'s observation in the addition of 2-furyl-metal derivatives to glyceraldehyde acetonide [8]. The cyclic model of *Cram*'s rule could be used to discuss those results, *i.e.* 5-ring chelation with Li and 6-ring chelation with Zn.

Scheme 3



7 X = Br, R = H[7])
8 X = R = H
9 X = H, R = (*t*-Bu)Me_2Si

10 R = Ph
((*E*)/(*Z*) *ca.* 1:1)
11 R = CO_2Me
(only (*E*))

12 M =			**13**
Li	2	: 1	
MgBr	1	: 1	
ZnCl	1	: 2.5	
$Ti(OCHMe_2)_3$	3.5	: 1	

At this point, we have shown that the dibromide **2** can be used for a number of conversions with introduction of new substituents in the 4-position of the butanoic-acid moiety. A crucial step is the subsequent hydrogenation of the dioxinone double bond with regeneration of a stereogenic center in the 6-position of the ring. We have shown only in *one* case[9]) that such a hydrogenation may be highly diastereoselective [2]. It turns out that catalytic (Pd/C) hydrogenation (AcOEt, 25°) removes the 5-bromo substituent

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[6]) Saponification of the acetate group in **5** was not tried, but may be tricky due to competing acetal hydrolysis.

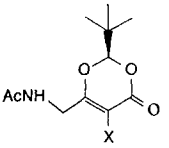
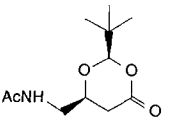
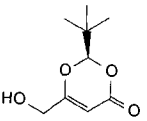
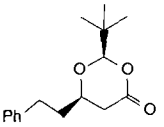
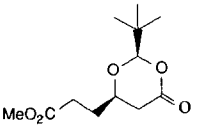
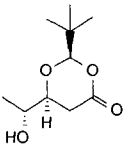
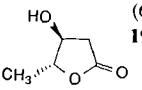
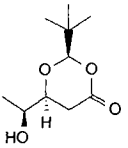
[7]) The products thus accessible are possible precursors to natural products containing quaternary stereogenic centers such as frontaline [6] or malyngolide [7].

[8]) The methylzinc reagent was generated *in situ* by adding $ZnCl_2$ to MeLi, so that LiCl was also present in the reaction mixture. The titanium reagent gave the highest selectivity, but the products were isolated in poor yield.

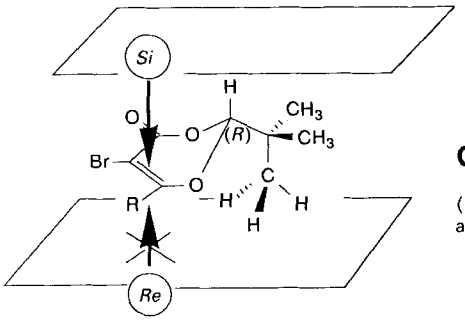
[9]) A similar 1,3-induction in a catalytic hydrogenation of an exocyclic double bond was also demonstrated in one case [3].

first (2–3 h at normal pressure). To remove the HBr formed, the reaction is carried out in the presence of 2–3 equiv. of Et_3N. The dioxinone double bond is hydrogenated only very slowly under these conditions ($\geq$ 24 h). In most cases, we have used high H_2 pressure (30 atm) in a steel autoclave to do both steps at once (10–15 h, with stirring). The examples are collected in *Table 1*. In no case did we observe formation of two diastereoisomeric products by 90-MHz ^{1}H-NMR spectroscopy. Thus, for practical purposes, hydrogenation is a totally selective method of regenerating the stereogenic center in the 6-position of the dioxane system. As shown by NMR comparison and in two cases (**3**, **12**) by chemical

Table 1. *Catalytic Hydrogenations of the Dioxinones* **3**, **7**, *and* **10–13.** If not stated otherwise, the reactions were carried out in AcOEt in the presence of several equiv. of Et_3N.

Starting material	Reaction conditions	Product	Yield of purified product [%]
3	1 atm AcOH AcOAc 16 h		**14** (X = H, Br) Mixture of brominated (**14a**) and non-brominated product (**14b**) 52
14a + **14b**	30 atm 30 h		**15** Quantitatively hydrolyzed to (+)-(*S*)-gabob of 85% ee [9] 76
7	1 atm 12 h		**8** ≥ 50
10	30 atm 60 h		**16** Comparison with hydrogenated benzylation product of dienolate [2] from **i**, see *Footnote 3* 90
11	30 atm 66 h		**17** 91
12	30 atm 16 h		**18** Treatment with H^+ (THF/H_2O) gave  (60%) **19** (*cf.* [10]) 82
13	30 atm 16 h		**20** 72

correlation, the hydrogenation takes place from the face opposite to the *t*-Bu group (see *Formulae* **15–20** in *Table 1*). This result is obvious only in a very naive '*trans*-to-the-*t*-Bu-group' analysis. Inspection of a model, or even better of a space-filling presentation produced with a molecular modelling program reveals that the two diastereotopic faces of the dioxinone double bond are not all that different in their steric hindrance to the approach of a reagent or to adsorption on a surface, see **C**. An extensive discussion of this question will be given in a forthcoming paper on *Michael* additions to dioxinones.



C

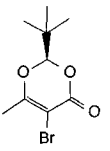
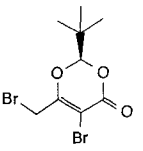
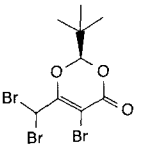
(relative topicity of attack *ul*-1.3)

We thank the Nihon University for financing *Y.N.*'s leave of absence. For advice and many fruitful discussions, we are indebted to *J. Zimmermann*. The *BASF-Aktiengesellschaft* (Ludwigshafen, FRG) and *ICI* (Billingham, GB) supplied generously pivalaldehyde and PHB, respectively. We gratefully acknowledge the work done in our Kilo laboratory (Mr. *K. Job*) providing hydroxybutanoic acid from PHB.

Experimental Part

General. All solvents for reactions were of *purissimum* quality. Unless otherwise stated, org. extracts were dried with $MgSO_4$ and concentrated by using a rotary evaporator. Buffer soln. of pH 7 was prepared by dissolving NaH_2PO_4 (85 g) and NaOH (14.5 g) in H_2O (950 ml). Flash chromatography (FC): *Fluka Kieselgel 60* (silica, mesh size 0.040-0.063). M.p.: *Büchi Tottoli* melting point apparatus and are uncorrected. $[\alpha]_D$: *Perkin-Elmer 241* polarimeter; $CHCl_3$ soln. at 25°; *c* in g/100 ml. IR spectra: *Perkin-Elmer 297;* $CHCl_3$ soln. ^1H- and ^{13}C-NMR spectra: *Varian EM-390* (90 MHz) or *Bruker WH 300* (300 MHz) and *Varian CFT-20* instrument, resp.; TMS as internal standard, $CDCl_3$ solns. Mass spectra: at 70 eV with *Hitachi-Perkin-Elmer RM V6M* instrument.

Table 2. *Bromination of the Dioxanone* **1** *with NBS* (cat. AIBN, CCl_4 reflux)

Entry	NBS [equiv.]	Reaction time [h]	 **21**		 **2**		 **22**
1	2.1	1.5	4	:	1		
2	3.2	1.75	3	:	2		
3	2.1+1.05	2+2			3	:	1
4	3.8	4.5	1	:	4.5	:	1
5	3.6	6	2	:	6	:	1
6	4.5	3	2	:	3		
7	4.5	6			1	:	4

Mono- and Dibromide **21** *and* **2**, *respectively, and (2*R*)-5-Bromo-2-(*tert*-butyl)-6-(dibromomethyl)-2*H*,4*H*-1,3-dioxin-4-one* (**22**). Dioxanone **1** (1.0 g, 5,8 mmol), NBS (3,9 g, 22 mmol), and 2,2'-azobisisobutyronitrile (AIBN; 30 mg) were refluxed in CCl_4 (20 ml) for 4,5 h. The mixture was cooled to 0°, filtered, and evaporated. The residue was purified by FC (CH_2Cl_2/hexane 3:1) to give **2** as an oil (907 mg, 48%). Besides **2**, the compounds **21** and **22** are present in the crude mixture (elution order **22, 2, 21**).

The reaction can be carried out on much larger scale [3], but the chromatographic separation of **2** is difficult on a > 4-g scale. The reaction conditions and product ratios (determined by ^{1}H-NMR) are summerized in *Table 2*. The above procedure corresponds to *Entry 4*. The oily tribromide **22** is the main product with longer reaction times, see *Entry 7*. Compounds **2** and **21** have been characterized in [3].

22: IR ($CHCl_3$): 3020*w*, 2980*w*, 2970*w*, 1755*s*, 1600*m*, 1340*s*, 1170*m*, 1085*s*. ^{1}H-NMR (300 MHz): 1.14 (*s*, *t*-Bu); 5.23 (*s*, OCHO); 6.63 (*s*, BrCHBr). ^{13}C-NMR (75 MHz): 23.76; 30.49; 34.74; 89.25; 107.54; 157.08; 163.02. MS: 410 (0.7, $M^{+\cdot}$ + 3), 408 (2.1, $M^{+\cdot}$ + 1), 406 (2.1, $M^{+\cdot}$ − 1), 404 (0.7, $M^{+\cdot}$ − 3), 322 (11), 320 (11), 242 (12), 235 (14), 233 (14), 149 (12), 147 (13), 123 (29), 121 (31), 57 (100), 43 (33), 42 (18), 41 (26). Anal. calc. for $C_9H_{11}Br_3O_3$: C 26.57, H 2.72; found: C 25.91, H 2.68.

*(2*R*)-6-(Azidomethyl)-5-bromo-2-(*tert*-butyl)-2*H*,4*H*-1,3-dioxin-4-one* (**3**). Dibromide **2** (2.52 g, 7.7 mmol) and NaN_3 (552 mg, 8.5 mmol) were stirred in DMF (15 ml) at 25° for 30 min. H_2O (5 ml) was added and the mixture extracted with Et_2O (3 × 50 ml). The org. layer was dried and evaporated, the residue purified by FC (CH_2Cl_2/hexane 3:1) to give pure **3** (1.59 g, 72%). M.p. 98–99° (Et_2O/hexane). $[\alpha]_D$ = − 13.0° (*c* = 0.79). IR ($CHCl_3$): 3020*w*, 2990*w*, 2970*w*, 2110*s*, 1760*s*, 1745*s*, 1610*m*, 1345*s*, 1080*s*. ^{1}H-NMR (300 MHz): 1.10 (*s*, *t*-Bu); 4.14, 4.29 (*AB*, *J* = 15.1, CH_2); 5.22 (*s*, OCHO). ^{13}C-NMR (75 MHz): 23.82; 34.41; 50.28; 93.20; 106.86; 158.01; 164.97; MS: 291 (1.0, $M^{+\cdot}$ + 1), 289 (1.2, $M^{+\cdot}$ − 1), 205 (28), 203 (28), 149 (98), 147 (98), 121 (20), 119 (20), 57 (100), 43 (35), 42 (21), 41 (67), 39 (24), 29 (47), 28 (44), 27 (28). Anal. calc. for $C_9H_{12}BrN_3O_3$: C 37.26, H 4.17, N 14.48; found: C 37.24, H 4.26, N 14.41.

*(2*R*)-5-Bromo-2-(*tert*-butyl)-2*H*,4*H*-1,3-dioxin-4-on-6-carboxaldehyde* (**6**). Dibromide **2** (610 mg, 1.9 mmol) and $AgNO_3$ (480 mg, 2.8 mmol) were stirred in MeCN (10 ml) at 25° for 1 h and refluxed at 80° for 2 h. The mixture was cooled to r.t., sat. NaCl soln. (0.5 ml) and Et_2O (50 ml) were added, the org. layer was dried and filtered. Evaporation gave a yellow solid which was purified by FC (CH_2Cl_2/hexane 10:1) to give **6** (334 mg, 68%). The reaction can also be done on large scale with mixtures containing mono- and dibromide (**21** and **2**). The aldehyde **6** is easily separated from **21** by FC (eluted first).

6: M.p. 80–82° (hexane/Et_2O), $[\alpha]_D$ = − 12° (*c* = 2.32). IR ($CHCl_3$): 3020*w*, 2980*m*, 2970*m*, 2910*w*, 2880*s*, 1756*s*, 1702*s*, 1580*w*, 1485*w*, 1350*s*, 1160*s*, 1070*s*. ^{1}H-NMR (300 MHz): 1.11 (*s*, *t*-Bu); 5.18 (*s*, OCHO); 10.00 (*s*, CHO). ^{13}C-NMR (75 MHz): 23.84; 34.71; 103.52; 107.11; 155.22; 183.36; 188.77. MS: 264 (1.8, $M^{+\cdot}$ + 1), 262 (1.8, $M^{+\cdot}$ − 1), 149 (44), 147 (45), 87 (100), 69 (23), 57 (98), 41 (38), 29 (20). Anal. calc. for $C_9H_{11}BrO_4$: C 41.09, H 4.21; found: C 40.83, H 4.07.

*(2*R*)-5-Bromo-2-(*tert*-butyl)-6-(hydroxymethyl)-2*H*,4*H*-1,3-dioxin-4-one* (**7**). A soln. of $Zn(BH_4)_2$ (7 ml, prepared from $ZnCl_2$ (1 g) and $NaBH_4$ (675 mg) in 50 ml of Et_2O) was added to a soln. of **6** (1.29 g, 4.9 mmol) in Et_2O (5 ml). After 24 h at r.t., the mixture was treated with H_2O (5 ml). The Et_2O layer was separated, dried, filtered, and evaporated. The residue was purified by FC (CH_2Cl_2/Et_2O 10:1) to give **7** (1.0 g, 77%) as an oil. $[\alpha]_D$ = − 152.1° (*c* = 1.17). IR ($CHCl_3$): 3610*w*, 3480*w*, 3020*w*, 2980*m*, 2970*m*, 1740*s*, 1610*m*, 1470*m*, 1340*s*, 1080*s*. ^{1}H-NMR (300 MHz): 1.09 (*s*, *t*-Bu); 1.88 (br. *s*, OH); 4,48, 4.62 (*AB*, *J* = 15.4); 5.18 (*s*, OCHO). ^{13}C-NMR (75 MHz): 23.97; 34.55; 61.01; 91.03; 106.85; 158.82; 168.58. MS: 266 (0.1, $M^{+\cdot}$ + 1), 264 (0.1, $M^{+\cdot}$ − 1), 235 (0.5), 233 (0.4), 181 (9), 180 (11), 179 (9), 178 (11), 87 (100), 69 (21), 57 (69), 41 (34), 31 (25). Anal. calc. for $C_9H_{13}BrO_4$: C 40.78, H 4.98; found: C 40.66, H 5.11.

*(2*R*)-5-Bromo-2-(*tert*-butyl)-6-(2-phenylethenyl)-2*H*,4*H*-1,3-dioxin-4-one* (**10**, (*E*)/(*Z*)-mixture). A THF soln. (5 ml) of (benzylidene)triphenylphosphorane (prepared from (benzyl)triphenylphosphonium bromide (265 mg, 0.66 mmol) and BuLi (0.4 ml, 0.61 mmol) in hexane) was added to a soln. of **6** (145 mg, 0.55 mmol) in THF. After 2 h at r.t., the mixture was filtered and evaporated. The residue was purified by FC (CH_2Cl_2/hexane 3:1) to give **10** as a solid (140 mg, 75%, 1:1 mixture of (*E*)- and (*Z*)-isomer). Recrystallization from hexane can be used to separate the isomers. M.p. ((*E*)-isomer) 177–179°. $[\alpha]_D$ = − 346.8° (*c* = 0.95; of (*E*)/(*Z*)-mixture). IR ($CHCl_3$; (*E*)/(*Z*)-mixture): 3020*w*, 3010*w*, 2980*w*, 2960*w*, 1730*s*, 1620*s*, 1580*m*, 1555*s*, 1340*s*, 1090*s*, 970*m*, 690*m*. ^{1}H-NMR (300 MHz; (*E*)-isomer): 1.16 (*s*, *t*-Bu); 5.19 (*s*, OCHO), 7.12 (*d*, J_{trans} = 16, HC=CH); 7.37 (*d*, *J* = 16.0), 7.40–7.55 (arom. H). ^{1}H-NMR (90 MHz, (*Z*)-isomer): 0.77 (*s*, *t*-Bu); 4.93 (*s*, OCHO); 6.39 (*d*, J_{cis} = 12.0, HC=CH); 7.05 (*d*, *J* = 12.0), 7.3 (*m*, arom. H). ^{13}C-NMR (75 MHz, (*E*)-isomer): 24.08; 34.64; 92.70; 105.85; 117.44; 128.25; 128.65; 129.07; 130.65; 134.52; 141.05; 160.10; 163.21. MS ((*E*)/(*Z*)-mixture): 339 (8, $M^{+\cdot}$ + 2), 338 (12, $M^{+\cdot}$ + 1), 337 (5, $M^{+\cdot}$), 336 (6, $M^{+\cdot}$ − 1), 253 (4), 252 (6), 251 (4), 250 (9), 172 (26), 131 (100), 103 (25). Anal. calc. for $C_{16}H_{17}BrO_3$ ((*E*)-isomer): C 56.99, H 5.08; found: C 56.87, H 5.07.

*Methyl (E)-3-[(2'R)-5'-Bromo-2'-(*tert*-butyl)-4'-oxo-2'*H*,4'H-1',3'-dioxin-6'-yl]acrylate* (**11**). The aldehyde **6** (150 mg, 0.59 mmol) was added to a soln. of [(methoxycarbonyl)methylidene]triphenylphosphorane (218 mg, 0.65 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at r.t. for 2 h, filtered, and evaporated. The residue was purified by FC (CH_2Cl_2/hexane 9:1) to give **11** (163 mg, 90%). M.p. 130.5–131.5° (hexane/Et_2O), $[\alpha]_D = -287.9°$ ($c = 1.13$). IR ($CHCl_3$): 3020*w*, 2980*w*, 2960*w*, 1735*s*, 1630*w*, 1562*m*, 1350*s*, 1300*s*, 1280*s*, 1170*s*, 1090*s*, 975*m*. ^{1}H-NMR (300 MHz): 1.11 (*s*, *t*-Bu); 3.84 (*s*, $COOCH_3$); 5.19 (*s*, OCHO); 6.59, 7.60 (*d*, $J = 16.0$, =CH). ^{13}C-NMR (75 MHz): 23.95; 34.63; 52.44; 98.12; 106.32; 128.71; 132.52; 159.00; 160.66; 165.22. MS: 320 (7, $M^{+\cdot} + 1$), 318 (7, $M^{+\cdot} - 1$), 234 (26), 232 (23), 113 (100), 57 (70), 41 (21). Anal. calc. for $C_{12}H_{15}BrO_5$: C 45.16, H 4.74; found: C 45.30, H 4.82.

*(2R,1'R)- and (2R,1'S)-5-Bromo-2-(*tert*-butyl)-6-(1'-hydroxyethyl)-2*H*,4*H*-1,3-dioxin-4-one* (**12** and **13**, resp.). A) *Addition of MeZnCl to* **6**. To an Et_2O soln. (5 ml) of MeMgBr (0.6 ml, 0.7 mmol) was added well dried $ZnCl_2$ (95 mg, 0.7 mmol) at −78°, and the resulting soln. was stirred for 20 min. Aldehyde **6** (184 mg, 0.7 mmol) in Et_2O (2 ml) was added, and the mixture was stirred at −78° for 2 h. The reaction was stopped by the addition of pH 7 buffer soln. Workup and purification by FC (CH_2Cl_2/Et_2O 4:1) afforded a 2:5 mixture (by ^{1}H-NMR) **12**/**13** (84 mg, 43%).

B) *Addition of MeLi to* **6**. To a soln. of MeLi (1.6 mmol in 9 ml of Et_2O) was added **6** (400 mg, 1.5 mmol in 2 ml of Et_2O), and the mixture was stirred at −78° for 2 h. The reaction was quenched with pH 7 buffer soln. and worked up. Purification by two FC (first FC with CH_2Cl_2, second FC with hexane/Et_2O 2:1) gave pure **12** (158 mg, 38%) and **13** (69 mg, 16%).

12: Oil, $[\alpha]_D = -173°$ ($c = 0.80$). IR ($CHCl_3$): 3600*w*, 3470*w*, 3010*w*, 2980*m*, 2960*m*, 1750*s*, 1735*s*, 1600*m*, 1340*s*, 1170*m*, 1085*s*. ^{1}H-NMR (300 MHz): 1.09 (*s*, *t*-Bu); 1.46 (*d*, $J = 6.7$, CH_3); 2.05 (br. *s*, OH); 5.00 (br. *q*, $J = 6.5$, MeC*H*O); 5.16 (*s*, OCHO). ^{13}C-NMR (75 MHz): 19.62; 23.89; 34.53; 66.56; 90.00; 106.52; 159.20; 171.17. MS: 194 (15), 192 (14), 87 (100), 69 (19), 57 (18), 45 (59). Anal. calc. for $C_{10}H_{15}BrO_4$: C 43.04, H 5.42; found: C 42.97, H 5.58.

13: M.p. 124.0–124.5° (hexane/Et_2O). $[\alpha]_D = -206.8°$ ($c = 0.91$). IR ($CHCl_3$): 3590*w*, 3480*w*, 3010*w*, 2980*w*, 2960*w*, 1750*s*, 1735*s*, 1600*m*, 1340*s*, 1170*m*, 1085*s*. ^{1}H-NMR (300 MHz): 1.10 (*s*, *t*-Bu); 1.43 (*d*, $J = 6.7$, CH_3); 2.13 (*d*, $J = 7.3$, OH); 4.96 (*quint.*, $J = 6.7$, MeC*H*O); 5.10 (*s*, OCHO). ^{13}C-NMR (75 MHz): 20.01; 23.92; 34.62; 66.38; 90.61; 107.01; 159.00; 170.71. MS: 194 (16), 192 (16), 87 (100), 69 (21), 57 (29), 45 (78), 41 (76). Anal. calc. for $C_{10}H_{15}BrO_4$: C 43.03, H 5.42; found: C 42.75, H 5.46.

*N-{[(2R)-5-Bromo-2-(*tert*-butyl)-4-oxo-2*H*,4*H*-1,3-dioxin-6-yl]methyl}acetamide* (**14a**) *and N-{[(2R)-2-(*tert*-Butyl)-4-oxo-2*H*,4*H*-1,3-dioxin-6-yl]methyl}acetamide* (**14b**). Azide **3** (2.1 g, 7.2 mmol) was dissolved in AcOH/Ac_2O 10:1 (11 ml), 10% Pd (700 mg) was added, and the mixture was stirred under H_2 (1 atm) for 16 h, filtered, and evaporated. The residue was purified by FC (CH_2Cl_2/Et_2O 1:1) to yield **14a** (805 mg, 37%) and **14b** (250 mg, 15%).

14a: M.p. 130–131° (CH_2Cl_2/Et_2O). $[\alpha]_D = -10.4$ ($c = 1.14$). IR ($CHCl_3$): 3460*w*, 3010*w*, 2980*w*, 2970*w*, 1740*s*, 1685*s*, 1605*m*, 1510*m*, 1345*s*, 1080*s*. ^{1}H-NMR (300 MHz): 1.05 (*s*, *t*-Bu); 2.04 (*s*, CH_3CO); 4.14 (*dd*, $J = 17.0$, 5.9, 1 H, CH_2); 4.52 (*dd*, $J = 17.0$, 6.1, 1 H, CH_2); 5.13 (*s*, H–C(2)); 5.90 (br. *s*, NH). ^{13}C-NMR (75 MHz): 22.65; 23.82; 34.34; 40.67; 91.22; 106.60; 158.78; 167.29; 170.17. MS 308 (1.9, $M^{+\cdot} + 2$), 307 (1.2, $M^{+\cdot} + 1$), 306 (1.7, $M^{+\cdot}$), 305 (1.0, $M^{+\cdot} - 1$), 221 (19), 219 (18), 180 (22), 179 (98), 178 (23), 177 (100), 72 (73), 43 (80), 30 (80). Anal. calc. for $C_{11}H_{16}BrNO_4$: C 43.15, H 5.27, N 4.58; found: C 42.95, H 5.12, N 4.41.

14b: M.p. 157–158° (AcOEt). $[\alpha]_D = -185.4$ ($c = 1.09$). IR ($CHCl_3$): 3360*w*, 3120*w*, 2980*m*. 2970*m*, 1720*s*, 1670*s*, 1630*s*, 1530*s*, 1400*s*, 1370*s*, 1315*s*, 1280*s*, 1080*s*, 825*m*. ^{1}H-NMR (300 MHz): 1.05 (*s*, *t*-Bu); 2.06 (*s*, CH_3); 3.95 (*ddd*, $J = 17.6$, 5.6, 0.8, 1 H, CH_2); 4.21 (*ddd*, $J = 17.6$, 6.7, 1.2, 1 H, CH_2); 5.08 (*s*, OCHO); 5.40 (*s*, H–C(5)); 6.06 (*s*, NH). ^{13}C-NMR (75 MHz): 22.79; 23.85; 34.28; 39.98; 93.99; 106.37; 162.77; 170.37; 171.54. MS: 228 (1.7, $M^{+\cdot} + 1$), 227 (0.7, $M^{+\cdot}$), 158 (10), 142 (18), 141 (37), 128 (29), 113 (26), 100 (86), 99 (24), 73 (61), 72 (100), 43 (37), 30 (66). Anal. calc. for $C_{11}H_{17}NO_4$: C 58.14, H 7.57, N 6.16; found: C 57.55, H 7.56, N 6.25.

*N-{[(2R,4S)-2-(*tert*-Butyl)-6-oxo-1,3-dioxan-4yl]methyl}acetamide* (**15**) *and (S)-4-Amino-4-hydroxybutanoic Acid* (gabob). To a mixture of **14a** (94 mg, 0.31 mmol) and **14b** (51 mg, 0.22 mmol) in AcOEt (5 ml), 10% Pd/C (70 mg) and Et_3N (0.05 ml, 0.5 mmol) were added. Stirring under H_2 (30 atm) for 30 h, filtering, washing with H_2O, drying and evaporating gave a residue which was purified by FC (Et_2O): 92 mg (76%) of **15** (oil). $[\alpha]_D = -14.2°$ ($c = 0.93$). IR ($CHCl_3$): 3670*w*, 3460*w*, 3350*w*, 3010*m*, 2980*m*, 2960*m*, 1740*s*, 1675*s*, 1515*s*, 1370*m*, 1350*m*, 1245*s*, 990*s*. ^{1}H-NMR (300 MHz): 0.99 (*s*, *t*-Bu); 2.01 (*s*, CH_3); 2.45 (*dd*, $J = 17.7$, 9.7, H–C(5)); 2.68 (*dd*, $J = 17.7$, 5.3, H–C(5)); 3.34 (*dt*, $J = 14.3$, 6.3, NCH); 3.56 (*ddd*, $J = 14.3$, 6.3, 3.5, NCH); 4.08 (*m*, H–C(6)); 4.90 (*s*, H–C(2)); 5.80 (br. *s*, NH). ^{13}C-NMR (75 MHz): 23.10; 23.94; 33.10; 35.25; 43.09; 72.09; 107.75; 167.48; 170.42. MS: 230 (1.7, $M^{+\cdot} + 1$), 229 (0.6, $M^{+\cdot}$), 143 (30), 136 (62), 84 (100), 73 (62), 70 (22), 57 (49), 43 (21).

A soln. of **15** (293 mg, 1.3 mmol) in 4N HCl (5 ml) was refluxed for 2.5 h. H_2O was evaporated and the residue was dried under high vacuum to give the crude hydrochloride. The salt was dissolved in H_2O (10 ml) and adsorbed on acidic *Dowex 50 W × 8* (15 g). The resin was washed with distilled H_2O until neutral and then the free amino acid is eluted with 2N NH_3 in H_2O. Evaporation gave 160 mg of gabob. $[\alpha]_D = +18.1°$ ($c = 0.85$, H_2O; [9]: $-21.06°$ for (*R*)-gabob). ^{1}H-NMR (D_2O, 90 MHz): 2.33 (*d*, $J = 6.2$, H–C(2)); 2.60–3.23 (*m*, 2 H–C(4)); 3.93–4.30 (*m*, H–C(3)).

*(2*R,*6*R*)-2-(*tert*-Butyl)-6-(-2'-phenylethyl)-1,3-dioxan-4-one* (**16**). A soln. of **10** ((*E*/*Z*)-mixture; 213 mg, 0.63 mmol) in AcOEt (7 ml), 10% Pd/C (50 mg) and Et_3N (0.1 ml, 1 mmol) were stirred under H_2 (30 atm) for 60 h, filtered, washed with H_2O dried, and evaporated. The residue was purified by FC (CH_2Cl_2/Et_2O 10:1) to give **16** (150 mg, 90%). M.p. 68° (hexane/Et_2O). $[\alpha]_D = -10.4°$ ($c = 1.15$), identical in all respects with the material prepared by another route[10]). IR ($CHCl_3$): 3080*w*, 3060*w*, 3010*w*, 2980*m*, 2960*m*, 2880*w*, 1740*s*, 1600*w*, 1485*m*, 1350*m*, 985*s*, 700*m*. ^{1}H-NMR (300 MHz): 1.01 (*s*, *t*-Bu); 1.84, 1.96 (*m*, $PhCH_2CH_2$); 2.4 (*dd*, $J = 17.7$, 10.6, H–C(5)); 2.60 (*dd*, $J = 17.7$, 4.5, H–C(5)); 2.78 (*m*, $PhCH_2$); 3.78 (*m*, H–C(6)); 4.86 (*s*, H–C(2)); 7.16–7.34 (*m*, arom. H). ^{13}C-NMR (75 MHz): 23.96; 30.90; 35.32; 36.26; 36.90; 72.72; 108.45; 126.19; 128.55; 140.75; 168.10. MS: 205 (53), 176 (30), 159 (94), 91 (100), 57 (21). Anal. calc. for $C_{16}H_{22}O_3$: C 73.25, H 8.45; found: C 73.04, H 8.79.

*Methyl 3-[(2'*R*,4'*R*)-2'-(*tert*-Butyl)-6'-oxo-1',3'-dioxan-4'-yl]propionte* (**17**). To a soln. of **11** (0.63 mg, 0.51 mmol) in AcOEt (5 ml) were added 10% Pd/C (30 mg) and Et_3N (0.1 ml, 1 mmol) and the mixture was stirred under H_2 (30 atm) for 60 h, filtered, washed with H_2O, dried, and evaporated. The residue was purified by FC (CH_2Cl_2) to give **17** (113 mg, 91%). M.p. 20–25° (hexane/Et_2O). $[\alpha]_D = +10.4°$ ($c = 1.15$). IR ($CHCl_3$): 3020*w*, 2980*w*, 2960*w*, 1740*s*, 1485*m*, 1440*m*, 1370*m*, 1350*m*, 1250*s*, 990*s*. ^{1}H-NMR (300 MHz): 0.98 (*s*, *t*-Bu), 1.94 (*m*, $MeO_2CCH_2CH_2$); 2.40 (*dd*, $J = 17.7$, 10.7, H–C(5)); 2.50 (*m*, $MeO_2CCH_2CH_2$); 2.67 (*dd*, $J = 17.7$, 4.5, H–C(5)); 3.69 (*s*, $COOCH_3$); 3.92 (*m*, H–C(6)); 4.88 (*s*, OCHO). ^{13}C-NMR (75 MHz): 23.86; 29.33; 30.39; 35.26; 36.13; 51.73; 73.00; 108.36; 167.76; 173.11. MS: 245 (0.5, $M^+ + 1$), 243 (0.8, $M^+ - 1$), 187 (12), 159 (55), 141 (61), 127 (29), 115 (20), 114 (100), 113 (27), 85 (45), 82 (23), 71 (46), 57 (48), 55 (40). Anal. calc. for $C_{12}H_{20}O_5$: C 59.00, H 8.25; found: C 58.67, H 7.92.

*(2*R,*6*S,*1'*R*)-2-(*tert*-Butyl)-6-(1'-hydroxyethyl)-1,3-dioxan-4-one* (**18**). A mixture of **12** (289 mg, 1 mmol), 10% Pd/C (100 mg), and Et_3N (0.15 ml, 1.5 mmol) was stirred under H_2 (30 atm) in AcOEt (10 ml) for 16 h. The mixture was filtered, washed with H_2O, dried, and evaporated. The residue was purified by FC (hexan/Et_2O 2:1) to give **18** (170 mg, 81%) as an oil (unstable upon storage, also in the NMR sample soln.). $[\alpha]_D = -32°$ ($c = 1.34$). IR ($CHCl_3$): 3600*w*, 3480*w*, 3010*w*, 2980*m*, 2960*m*, 2900*m*, 1740*s*, 1485*m*, 1370*m*, 1250*s*, 1000*s*, 985*s*. ^{1}H-NMR (300 MHz): 0.99 (*s*, *t*-Bu); 1.19 (*d*, $J = 6.4$, CH_3); 2.62 (*dd*, $J = 17.8$, 5,5 H–C(5)); 2,75 (*dd*, $J = 17.8$, 9.4, H–C(5)); 3.81 (*qd*, $J = 6.4$, 4.0, CHO); 3.99 (*ddd*, $J = 9.4$, 5.5, 4.0, H–C(6)); 4.93 (*s*, OCHO). ^{13}C-NMR (75 MHz): 14.75; 24.46; 35.69; 37.57; 74.18; 74.32; 109.64; 175.76. MS: 202 (0.1, $M^{+\cdot}$), 158 (2), 145 (5), 99 (100), 87 (33), 72 (48), 71 (36), 70 (33), 57 (93), 55 (22), 45 (37), 43 (84).

3-Hydroxy-4-pentanolide (**19**) *of (3*S,*4*R*)-3,4-dihydroxypentanoic Acid.* The crude product **18** (223 mg, 1.1 mmol) was heated at reflux in a mixture of 2N HCl (1 ml) and THF (3 ml) for 2 h. The mixture was cooled to 0°, neutralized with aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. Drying and evaporating gave a residue which was purified by FC (Et_2O): 87 mg (60%) of **19** as an oil. $[\alpha]_D = +10.0°$ ($c = 1.59$; [10]: $+10.87°$), IR and NMR: in agreement with those given in [10].

*(2*R,*6*S,*1'*S*)-2-(*tert*-Butyl)-6-(1'-hydroxymethyl)-1,3-dioxan-4-one* (**20**). A mixture of **13** (400 mg, 1.4 mmol), 10% Pd/C (100 mg), and Et_3N (0.15 ml, 1.5 mmol) was stirred under H_2 (32 atm) in AcOEt (10 ml) for 16 h. After filtering, washing with H_2O, drying, evaporating, and purifying by FC (CH_2Cl_2/Et_2O 4:1), 209 mg (72%) of **20** were obtained as an oil (like **18**, this compound is unstable, probably due to isomerizations caused by traces of acid). $[\alpha]_D = -31.8°$ ($c = 1.03$). IR ($CHCl_3$): 3600*w*, 3480*w*, 2980*w*, 2960*w*, 1740*s*, 1470*m*, 1250*s*, 990*s*. ^{1}H-NMR (300 MHz): 1.01 (*s*, *t*-Bu); 1.23 (*d*, $J = 6.3$, CH_3); 2.05 (br., OH); 2.62 (*m*, 2 H–C(5)); 3.76 (*m*, H–C(6) and C*H*OH); 4.93 (*s*, OCHO). ^{13}C-NMR (75 MHz): 17.84; 23.89; 32.19; 35.31; 69.30; 77.73; 107.83; 167.92. MS: 145 (42), 99 (59), 88 (11), 71 (11), 70 (23), 57 (100), 55 (12), 45 (43), 44 (50), 43 (50).

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[10]) *J. Zimmermann*, unpublished results, ETH Zürich, 1987 (*cf.* also [2]).

REFERENCES

[1] D. Seebach, S. Roggo, J. Zimmermann, in 'Stereochemistry of Organic and Bioorganic Transformations', Eds. W. Bartmann and K. B. Sharpless, VCH Verlagsgesellschaft, Weinheim, 1987, pp. 85–126.
[2] D. Seebach, J. Zimmermann, *Helv. Chim. Acta* **1986,** *68,* 1243.
[3] J. Zimmermann, D. Seebach, *Helv. Chim. Acta* **1987,** *69,* 1104.
[4] R. K. Boeckmann, Jr., A. J. Thomas, *J. Org. Chem.* **1982,** *47,* 2823.
[5] P. A. S. Smith, in 'Open-Chain Nitrogen Compounds', Benjamin, New York, 1966, Vol. II, Chapt. 15 D, p. 483ff.
[6] M.-C. Trinh, J.-C. Florent, C. Monneret, *J. Chem. Soc., Chem. Commun.* **1987,** 615, and ref. cit. therein.
[7] P. G. M. Wuts, M.-C. Cheng, *J. Org. Chem.* **1986,** *51,* 2844, and ref. cit. therein.
[8] K. Suzuki, Y. Yuki, T. Mukaiyama, *Chem. Lett.* **1981,** 1529.
[9] S. Takano, M. Yanase, Y. Sekiguchi, K. Ogasawara, *Tetrahedron Lett.* **1987,** *28,* 1783, and ref. cit. therein.
[10] S.-Y. Chen, M. Joullie, *J. Org. Chem.* **1984,** *49,* 2168; C. Papageogiou, C. Benezra, *Tetrahedron Lett.* **1984,** *25,* 6041.
[11] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2929.