94. Asymmetric Induction by Enantiotopically Differentiating *retro-Claisen* Reaction of Prochiral Bicyclic β-Diketones[1])

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Summary

The possibility of preparing cycloalkanones with an asymmetric β-C-atom by enantiotopically differentiating *retro-Claisen* reactions of bicyclic diketones **a** *(Scheme 1)* is tested with the decalin-1,8-diones **1** and **7**, as well as with the bicyclo[3.3.0]octane-2,8-diones **10** and **11**. Treatment of the reactive dione **1** with chiral tetra-alkyl titanate catalysts results in a low optical induction (13%, *Scheme 2*). Cleavage with the Na-salts of α-amino-alcohols and hydrolysis of the resulting amides or esters gives much better optical yields, reaching 86% ee with dione **1** and (−)-ephedrine *(Scheme 3)*. Almost as efficient is *N*-methylephedrine with 75% optical induction *(Scheme 5)*. Lower enantiotopical differentiation is, however, observed with (−)-ephedrine and diones **7** (44% ee), **10** (8% ee), and **11** (48% ee) (*Schemes 3* and *4*, *Table 1*), or with dione **1** and L-prolinol (37% ee) or (−)-2-amino-1-butanol (11% ee) *(Scheme 5, Table 2)*. The moderate chemical yields of these transformations (50–70%) can be ascribed to side-reactions of the ketones under the strongly basic conditions.

1. Introduction. – Part of a project, concerning the preparation of optically active compounds by differentiation of enantiotopical carbonyl groups [1] [3], is the *retro-Claisen* reaction of prochiral bicyclic β-diketones of type **a**, leading to cycloalkanones **b** with an asymmetric β-C-atom and a epimerized asymmetric α-C-atom *(Scheme 1)*. Since the optical resolution of ketones is rather difficult [4], the access to such substrates by stereo-differentiating reactions would be a valuable alternative[2]). In [9] we described an approach to this problem by acetalization of prochiral β-diketones followed by a *retro-Claisen* type fragmentation of the chiral monoacetals. Decalin-dione **1** is thus transformed to the optically pure cyclohexanones **2** and (+)-**3** *via* the monoacetal **4** in 63% overall yield *(Scheme 1)*.

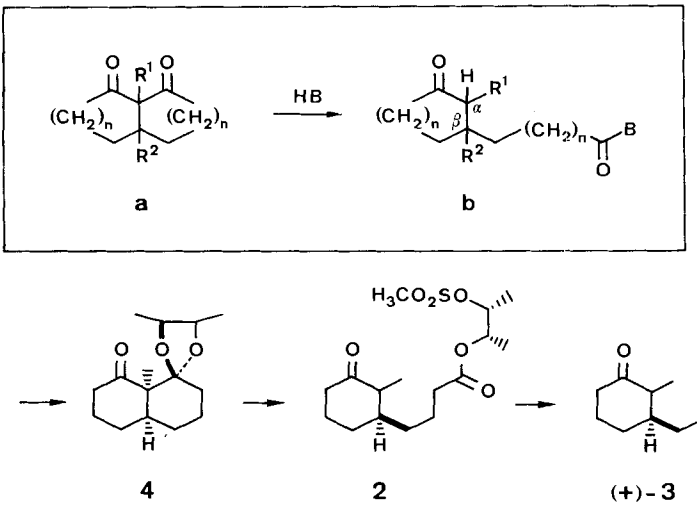
The topic of this communication is the direct cleavage of dione **1** and related substrates under enantiotopically differentiating reaction conditions.

2. Cleavage of Dione 1 with Chiral Base Catalysts. – As has been shown before, *cis*-decalin-dione **1** undergoes a smooth *retro-Claisen* reaction upon treatment with

[1]) These results are comprised in the Ph.D. thesis of *P. M.* [1]. The nomenclature and classification of stereo-differentiating reactions proposed by *Izumi & Tai* [2] are used in this communication.

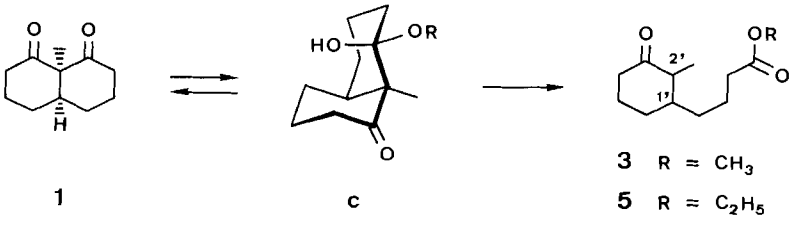
[2]) Optically active carbonyl compounds with an asymmetric β-C-atom have been obtained by 1,4-additions to α,β-unsaturated carbonyl compounds, either under enantioface-differentiating [5] [6] or under diastereo-face-differentiating [7] conditions, and by C(α)–C(β)-bond formation [8].

Scheme 1



K_2CO_3 in CH_3OH [3]. The ease of this transformation can be rationalized by a conformation of the hemiacetal intermediate **c**, which is stereoelectronically ideal for the subsequent cleavage [3] *(Scheme 2)*. Replacement of K_2CO_3 by a chiral catalyst should principally give rise to an optical induction either of the hemiacetalization, or of the cleavage of the racemic hemiacetal **c**. Unfortunately amines proved to be of insufficient base-strength for this reaction[3]). A slow *retro-Claisen* reaction, on the other hand, was observed with tetra-alkyl titanates[4]). Racemic ethyl ester **5** is obtained in 94% yield, when dione **1** is treated for 16 h with $Ti(OEt)_4$ in boiling EtOH *(Scheme 2)*[5]). With a chiral catalyst, obtained by mixing equimolar amounts of $Ti(OEt)_4$ and (+)-diethyl tartrate [11], a low enantiotopical differentiation, *ca.* 13% excess of (1′*S*)-enantiomer,

Scheme 2



[3]) No cleavage was observed with Et_3N, diisopropylethylamine, (−)-ephedrine, L-proline, and other amino-acids in boiling CH_3OH or in DMF.

[4]) Tetra-alkyl titanates are excellent catalysts for transesterifications of carboxylates [10], a process with some parallelism to the *retro-Claisen* reaction. Furthermore, chiral titanates are readily available and catalyze one of the most efficient enantio-differentiating processes known at present, the *Sharpless* epoxidation [11].

[5]) According to GC (see *Exper. Part*) ester **5** is a 66:44 mixture of 1′,2′-*trans*/*cis*-epimers. A single compound number is given to all ω-(2′-alkyl-3′-oxocycloalkyl)carboxylic-acid derivatives, which are generally 1′,2′-epimer mixtures.

Scheme 3

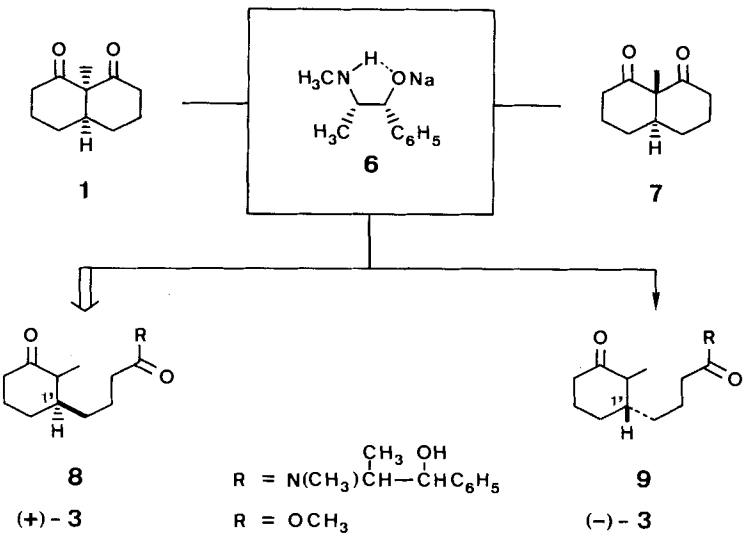


Table 1. *Cleavage with the Na-Salt* **6** *of (−)-Ephedrine (Schemes 3* and *4)*

Dione	Temp.	Reaction Time	Product	Yield (overall)	$[\alpha]_D$	Enantiom. Excess	Configuration of C(1')
1	r.t.	2 h	**3**	69%	+ 27.6°	78%[a])	*R*
1	0°	4 h	**3**	60%	+ 28.5°	81%[a])	*R*
1	− 20°	20 h	**3**	54%	+ 30.3°	86%[a])	*R*
7	r.t.	2 h	**3**	61%	+ 15.1°	43%[a])	*R*
7	0°	4 h	**3**	51%	+ 15.5°	44%[a])	*R*
10	r.t.	2 h	**16**	52%	− 5.7°	8%[b])	not determ.
11	r.t.	1 h	**17**	23%	− 37.7°	48%[b])	not determ.

[a]) Determined by $[\alpha]_D$-measurement[6])[9]).
[b]) Determined by acetalization with (2*R*,3*R*)-2,3-butanediol and GC analysis[12]).

was found[6]). This optical induction could not be improved by using benzene as solvent, or by using (2*R*,3*R*)-2,3-butanediol instead of tartrate as chiral auxiliary[7]).

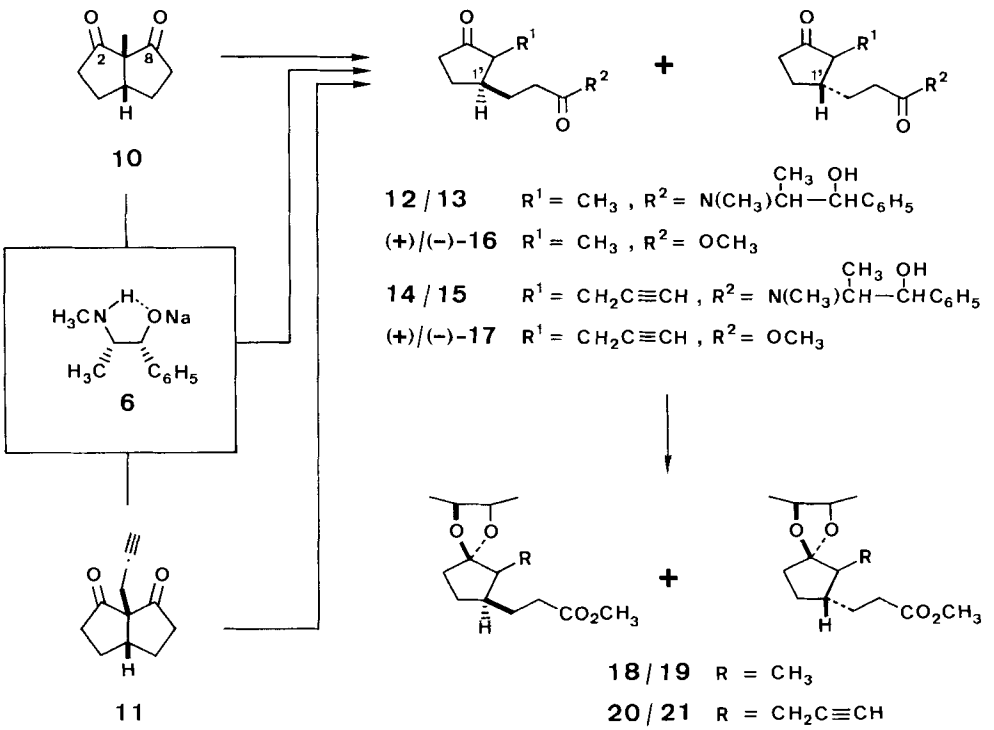
3. *Retro-Claisen* Reaction with the Na-Salt 6 of (−)-Ephedrine. – As the *retro-Claisen* reaction of dione **1**, catalyzed by chiral bases, gave no promising results, the attention was turned to the possibility of effecting enantiotopically differentiating *β*-di-

[6]) The enantiomeric excess was determined from the $[\alpha]_D$-value of methylester **3**, obtained from **5** by transesterification with CH_3ONa/CH_3OH. The $[\alpha]_D$-value of optically pure (+)-**3** ((1'*R*)-configuration) with the same 1',2'-epimer composition (*trans*/*cis* = 77:23, according to GC) [9] was used as reference. Acetalization of **3** with (2*R*,3*R*)-2,3-butanediol and GC analysis of the resulting acetal mixture has been successfully applied, to confirm the optical purity of (+)-**3** and (−)-**3** [9]. This method fails, however, if applied to the determination of the enantiomeric excess, because of the poor separation of the four diastereomeric acetals by capillary GC (see [9]). If applied to pure samples, the often criticized determination of optical purity by $[\alpha]_D$-measurement, gives consistent results of adequate accuracy (see *below*).

[7]) For an experimental description of these results see [1].

ketone cleavages with chiral nucleophiles[8]). After some unrewarding attempts with the salts of chiral alcohols, the Na-salt **6** of (−)-ephedrine emerged as suitable nucleophile. Treatment of either *cis*-decalin-dione **1** or the *trans*-isomer **7** with a solution of **6** in THF gave mixtures of the diastereomeric amides **8** and **9** (55–80% yield), which were transformed to mixtures of (+)- and (−)-**3**[9]) by hydrolysis with aqueous base and esterification with CH_2N_2 *(Scheme 3)*. The favoured product with 86% diastereomeric excess (de) starting from *cis*-dione **1** and 44% de from **7** is amide **8** with (1′*R*)-configuration. In the case of dione **1** a slight temperature dependence of the enantiotopical differentiation can be noted. The excess of enantiomer (+)-**3** has been determined from the $[\alpha]_D$-values[6])[9]) *(Table 1)*.

Scheme 4



Analogous cleavage of the bicyclo[3.3.0]octanes **10** and **11**[10]) with the salt **6** gave mixtures of the diastereomeric amides **12/13** and **14/15**, respectively, which were transformed to methyl esters **16**[11]) and **17**[11]) as above *(Scheme 4)*. The degree of enantioto-

[8]) The possibility of effecting an enantiotopically differentiating cleavage, catalyzed by K_2CO_3, in a chiral alcoholic medium was not prosecuted.

[9]) Ester **3** is a 75:25 mixture of 1′,2′-*trans*- and 1′,2′-*cis*-isomer[5]). Optically pure (+)-**3** ($[\alpha]_D = +35.1°$) with 75:25 isomer ratio, used as reference for the determination of optical purities[6]), was obtained from optically pure (+)-**3** with 77:23 isomer ratio ($[\alpha]_D = +34.7°$, [9]) by analogous base treatment and esterification (see *Exper. Part*). Slightly lower $[\alpha]_D$-values, 33.6° (77:23 isomer ratio) and 34.1° (75:25 isomer ratio), result from calculation, using the $[\alpha]_D$-values of pure (+)-*trans*-**3** (+27.8°) and 98% (−)-*cis*-**3** (−52.4°) [9].

[10]) The preparation of **10** and **11** is described in [12].

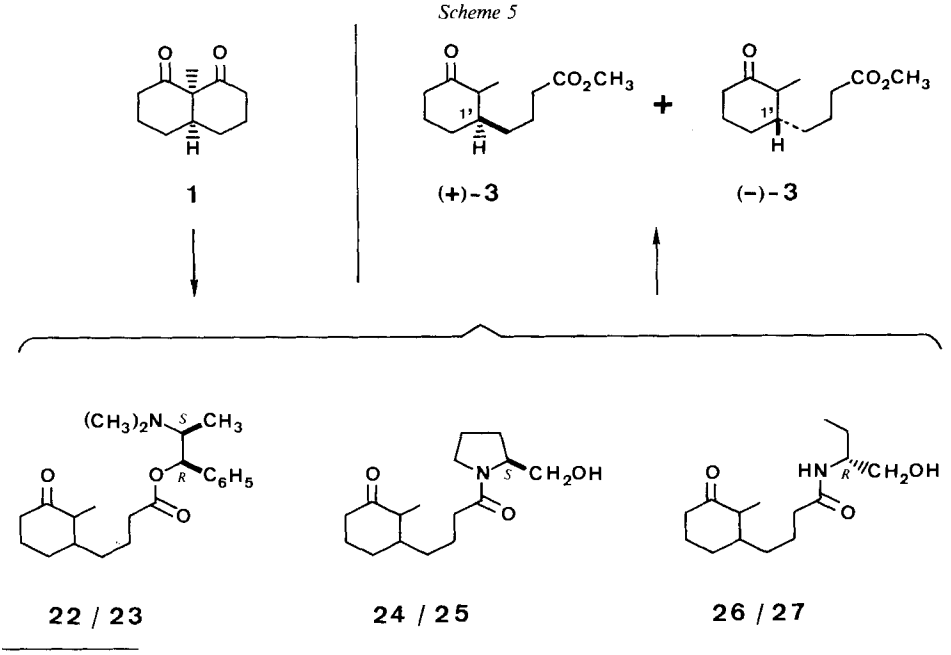
[11]) Mixtures of 1′,2′-*trans*- and 1′,2′-*cis*-isomers[5]).

pical differentiation, 8% in the case of the CH_3-substituted dione **10** and 48% for the propargyl derivative **11** *(Table 1)*, was determined by acetalization with (2*R*,3*R*)-2,3-butanediol and GC analysis of the resulting mixtures of the diastereomeric acetals **18**/**19**[11]) and **20**/**21**[11]) *(Scheme 4, Table 1)*[12]). The moderate-to-low yields of these two-step transformations (23%–70%, *Table 1*) have most probably to be ascribed to side reactions of the ketones under the rather harsh conditions of the cleavage and the amide hydrolysis. The keto-esters **3** and **5** are much more stable in hydroxylic solvents: CH_3OH/K_2CO_3 [3], CH_3OH/CH_3ONa [9], and $EtOH/Ti(OEt)_4$ (see *above*).

4. Cleavage of 1 with the Na-Salts of Chiral α-Amino-Alcohols. – The *retro-Claisen* reaction induced by the Na-salt **6** of (−)-ephedrine gave the highest optical yields with *cis*-decalin-dione **1**. The efficiency of other α-amino-alcohols was therefore tested with this system[13]). To prevent the adverse amide formation occuring with (−)-ephedrine, the Na-salt of (−)-*N*-methylephedrine was chosen as nucleophile. Methyl ester **3** was obtained by transesterification of the crude reaction mixture, containing the diastereomeric esters **22** and **23**. *(Scheme 5)*[14]. The optical induction with 75% excess of (1′*R*)-enantiomer (+)-**3** reaches almost the result obtained with the salt **6** derived from ephedrine *(Table 2)*.

Inferior enantiotopical differentiation was, however, found with the Na-salts of L-prolinol and (2*R*)-2-amino-1-butanol. Hydrolysis of the amide mixtures **24**/**25**, and

Scheme 5



[12]) Racemic **16** and **17** were obtained from **10** and **11**, respectively, by cleavage with aqueous base and esterification with CH_2N_2 *(Scheme 4)*. Acetalization gave 1:1 mixtures of **18**/**19** and **20**/**21**, which were used as references for the GC analyses of optically active material (see *Exper. Part*).

[13]) Cleavage of diones **7** and **10** with the salts of L-proline and (−)-2-amino-1-butanol gave in fact inferior results [1] compared to those found with **1** (see *below*).

[14]) Most of the *N*-methylephedrine could be recovered (see *Exper. Part*).

Table 2. *Cleavage of* **1** *with the Na-Salts of α-Amino-Alcohols (Schemes 3 and 5)*

Amino-Alcohol	Temp.	Reaction Time	Product	Yield (overall)	$[a]_D$	Enantiom. Excess	Configuration of C(1')
(−)-Ephedrine	0°	4 h	**3**	60%	+ 28.5°	81%[a])	*R*
(−)-Ephedrine	r.t.	2 h	**3**	69%	+ 27.6°	78%[a])	*R*
(−)-*N*-Methylephedrine	r.t.	18 h	**3**	48%	+ 26.1°	75%[a])	*R*
L-Prolinol	0°	1 h	**3**	49%	− 13.1°	37%[a])	*S*
(−)-2-Amino-1-butanol	0°	1 h	**3**	57%	+ 4.1°	11%[a])	*R*

[a]) Determined by $[\alpha]_D$-measurement[6])[9]).

26/**27** followed by esterification gave ester **3**. A 37% excess of (1'*S*)-enantiomer (−)-**3** was obtained with the salt of L-proline, a 11% excess of (+)-**3** with the salt of (2*R*)-2-amino-1-butanol *(Scheme 5, Table 2)*.

5. Discussion. – The *retro-Claisen* reaction of *cis*-decalin-dione **1** with the Na-salts of (−)-ephedrine and (−)-*N*-methylephedrine proceed with an enantiotopical differentiation ranging from 87.5:12.5 (75% ee) to 93:7 (86% ee, *Tables 1* and *2*). The energy differences of the corresponding diastereomeric transition states or intermediates therefore definitely surpass the limit of 1 kcal/mol, which is generally considered the critical value insuring the possibility of a sound rationalization. However, the cleavage of **1** is a complex process, and it is rather difficult to decide, which intermediate or transitionstate is responsible for the enantiotopical differentiation. It is in fact conceivable, that the net optical induction results from contributions of several processes, including side reactions (see overall yields, *Tables 1* and *2*). These difficulties become insuperable, if an explanation including the results of the other diones, **7**, **10**, and **11**, is sought for.

Some conclusions can all the same be drawn from the data of *Tables 1* and *2*. In contrary to the cleavage in alcoholic media catalyzed by weak bases, which proceeds only with *cis*-dione **1** *(Scheme 2)* [3], comparable rates for **1** and its *trans*-isomer **7** are observed with Na-alcoholates in THF. It seems therefore, that with strong nucleophiles the rate-determining step is the addition to the carbonyl group and not the subsequent fragmentation[15]). The fact, that the sense and to some extent also the magnitude of the optical induction is the same with (−)-ephedrine and (−)-*N*-methylephedrine, implies, that in the case of (−)-ephedrine, the carbonyl group is also attacked by the O-atom, and that the amides **8** and **9** *(Scheme 3)* are formed rather by rearrangement of the primarily formed esters, than by a direct attack of the N-atom with (*S*)-configurated *α*-C-atom[16]). This point is further corroborated by the strong influence on the enantiotopical differentiation exerted by the chirality of the O-substituted C-atom, which is evidenced by the low optical induction found with the primary alcohols L-prolinol (37%), (−)-2-amino-1-butanol (11%), and (−)-2-methyl-1-butanol (0%, [14]). Interestingly, L-prolinol with (*S*)-configuration of the *N*-substituted C-atom induces the (1'*S*)-configuration of **3**, while (+)-**3** ((1'*R*)-configuration) is formed in excess with

[15]) In the case of unsymmetrical *β*-diketones, the regioselectivity of the cleavage has been found to be governed by steric influences of the addition to the carbonyl group [13].

[16]) An attempt to explain the enantiotopical differentiation by an attack of the N-atom of (−)-ephedrine salt **6** is given in [1].

(2*R*)-2-amino-1-butanol[17]). It is therefore possible, that the N-substituted C-atom of (−)-ephedrine and (−)-*N*-methylephedrine, having (*S*)-configuration, has a weakly attenuating effect on the magnitude of enantiotopical differentiation, which is dominated by the (*R*)-configurated O-substituted C-atom. The same sense of enantiotopical differentiation is also observed, when dione **1** is acetalized with (2*R*,3*R*)-2,3-butanediol [3].

In comparison with the fragmentation of monoacetalized dione **1**, which gives optically pure (+)-**3** in 63% overall yield *(Scheme 1)* [9], the *retro-Claisen* reaction of **1** with the Na-salts of ephedrine and *N*-methylephedrine, giving (+)-**3** in 75–85% optical purity and in 50–70% yield, seems inferior at a first glance. Some advantages of this direct cleavage, especially for large-scale preparations, should, however, be noted. While the optical purity achieved in the monoacetal variant is based on the chromatographic separation of the diastereomeric acetals, crystallization of the amides **8** and **9** *(Scheme 3)* or of the esters **22** and **23** *(Scheme 5)* most probably improves the optical purity of the product obtained by direct cleavage. It is furthermore conceivable, that other chiral nucleophiles like *pseudo*-ephedrine or 2-amino-1-phenylethanol might improve the enantiotopical differentiation. The use of such less readily available chiral auxiliaries is justifiable, since they can be recovered easily. The costly (2*R*,3*R*)-2,3-butanediol on the other hand, used for the monoacetalization of dione **1**, is destroyed in the course of the *β*-ketoacetal fragmentation [9].

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Experimental Part

General Remarks. See [3] and [9]. *Materials.* (2*R*,3*R*)-2,3-Butanediol, (−)-ephedrine, (−)-*N*-methylephedrine, (+)-diethyl tartrate, and L-prolinol have been purchased from *Fluka AG*, Buchs, (−)-(2*R*)-2-amino-1-butanol of 95% opt. purity from *BASF AG*, Ludwigshafen. For the preparation of the diketones **1**, **7**, **10**, and **11** see [12].

1. Preparation of Reference Compounds. – 1.1. *Methyl 4-[(1′R)-2′-Methyl-3′-oxocyclohexyl]butyrate* (**3**). Optically pure (+)-**3** (1′,2′-*trans*/1′,2′-*cis* 78:22, $[\alpha]_D = +34.7°$, see [9], 49 mg, 0.231 mmol) was treated for 4 h in 5 ml of 2N aq. NaOH/dioxane 2:1 *(v/v)* at r.t. (Ar). After acidification with 1N HCl the product was isolated by extraction with Et_2O. The crude acid was dissolved in Et_2O and treated with an excess of ethereal CH_2N_2. Chromatography (5 g of silica gel, hexane/Et_2O 1:1) gave 45 mg (91%) of (+)-**3**, mixture of epimers: 2′*R(trans)*/2′*S(cis)* 75:25, according to GC (see [9]), $[\alpha]_D = +35.1°$ ($c = 2.14$, $CHCl_3$).

1.2. *(●)-Methyl 3-(2′-Methyl-3′-oxocyclopentyl)propionate* (**16**). A solution of *1-methylbicyclo[3.3.0]-octane-2,8-dione* (**10**) (99 mg, 0.652 mmol) in 5 ml of 2N aq. NaOH/dioxane 2:1 (*v/v*) was stirred for 2 h at r.t. under Ar. The mixture was acidified with 1N HCl and worked up with Et_2O. The crude acid was treated with an excess of ethereal CH_2N_2. Chromatography (silica gel, hexane/Et_2O 1:1) gave 107 mg (89%) of (±)-**16**, mixture of 1′,2′-*trans*/*cis*-epimers, according to GC (*UCON*, 160°, 0.35 kg/cm^2): $t_R = 2.8$ min (94%, *trans*?), $t_R = 3.1$ min (6%). IR (CCl_4): 2960*m*, 2950*m*, 2930*m*, 2870*m*, 1738*s*, 1451*m*, 1434*m*, 1420*w*, 1408*m*, 1375*m*, 1353*m*, 1330*w*, 1306*w*, 1280*w*, 1220*m*, 1192*m*, 1162*s*, 1134*m*, 1080*w*, 1020*w*, 987*w*, 949*w*, 922*w*, 890*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 1.08 (*d*, $J = 6$, CH_3–C(2′)); 1.02–2.6 (*m*, 10H); 3.66 (*s*, CH_3O–C(1)). MS: 184 (2, M^+), 169 (1), 166 (2), 153 (15), 134 (2), 111 (12), 110 (40), *97* (100), 96 (11), 93 (5), 92 (6), 91 (6), 87 (6), 83 (7), 82 (7), 81 (9),

[17]) It has, however, to be noted, that reaction of *trans*-dione **7** with the Na-salt of L-prolinol leads to a slight excess (10%) of (1′*R*)-configurated product **3** [1].

79 (5), 74 (30), 69 (20), 68 (17), 67 (14), 59 (8), 55 (35), 53 (9), 43 (21), 41 (30), 39 (15). Anal. calc. for $C_{10}H_{16}O_3$ (184.23): C 65.19, H 8.75; found: C 65.25, H 8.74.

1.3. *Acetalization of (±)-***16**. A solution of (±)-**16** (98 mg, 0.53 mmol), (2*R*,3*R*)-2,3-butanediol (97 mg, 1.07 mmol), and TsOH·H_2O (10 mg) in benzene (10 ml) was boiled under reflux at a *Dean-Stark* trap for 4.5 h (Ar). The reaction was quenched with sat. $NaHCO_3$-solution and worked up with Et_2O. Chromatography (silica gel, hexane/Et_2O 2:1) gave 130 mg (95%) of a 1:1 mixture of acetals **18** and **19**, both *ca.* 9:1 mixtures of 7′,6′-*cis*/*trans*-epimers, according to GC (*UCON*, 140°, 0.35 kg/cm^2), **18**: t_R = 6.0 min (45.4%) and t_R = 7.1 min (4.5%), **19**: t_R = 6.3 min (44.2%) and t_R = 6.8 min (5.9%).

*Methyl (2′*R*,3′*R*,7′*R*)- and Methyl (2′*R*,3′*R*,7′*S*)-3-(2′,3′,6′-Trimethyl-1′,4′-dioxaspiro[4.4]non-7′-yl)propionate* (**18**/**19**). IR (CCl_4): 2970*s*, 2950*m*, 2930*m*, 2870*m*, 1740*s*, 1451*m*, 1434*m*, 1375*m*, 1350*w*, 1303*m*, 1285*w*, 1250*m*, 1193*m*, 1161*m*, 1145*m*, 1110*m*, 1091*m*, 1029*w*, 977*w*, 933*w*, 909*w*, 890*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 0.91 (*d*, *J* = 6, CH_3–C(6′)); 1.12–1.19 (*6 resolved signals*, CH_3–C(2′), CH_3–C(3′)); 1.0–2.5 (*m*, 10H); 3.28–3.62 (*m*, H–C(2′), H–C(3′)); 3.62 (*s*, CH_3O–C(1)). MS: 256 (2, M^+), 227 (9), 225 (2), 212 (2), 183 (1), 169 (15), 153 (7), 141 (5), *127* (100), 125 (10), 119 (4), 105 (4), 97 (11), 81 (7), 79 (7), 77 (4), 69 (16), 67 (7), 56 (18), 55 (39), 53 (6), 43 (15), 41 (21), 39 (9). Anal. calc. for $C_{14}H_{24}O_4$ (256.33): C 65.59, H 9.44; found: C 65.42, H 9.41.

1.4. *(±)-Methyl 3-[2′-(2″-Propynyl)-3′-oxocyclopentyl]propionate* (**17**). A solution of 1-(2′-propynyl)bicyclo[3.3.0]octane-2,8-dione (**11**) (122 mg, 0.693 mmol) in 5 ml of 2N aq. NaOH/dioxane 2:1 (*v*/*v*) was stirred for 2 h at r.t., acidified with 1N HCl, and worked up with Et_2O. The crude acid (192 mg) was treated with an excess of ethereal CH_2N_2. Chromatography (silica gel, hexane/Et_2O 1:1) afforded 136 mg (94%) of (±)-**17**, mixture of 1′,2′-*trans*/*cis*-epimers, according to GC (*UCON*, 160°, 0.35 kg/cm^2): t_R = 4.2 min (9%, *cis*?), t_R = 6.7 min (91%). IR (CCl_4): 3306*m*, 2950*m*, 2930*m*, 2860*w*, 2110*w*, 1740*s*, 1450*w*, 1433*m*, 1422*m*, 1406*m*, 1357*w*, 1335*w*, 1279*m*, 1252*m*, 1194*m*, 1165*m*, 1143*m*, 1080*w*, 1015*w*, 986*w*, 924*w*, 889*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.36–1.52, 1.57–1.73, and 1.82–1.99 (3*m*, 1H each); 1.94 (*t*, *J* = 2.7, H–C(3″)); 2.04–2.28 (*m*, 4H); 2.34–2.57 (*m*, 2 H–C(4′), H–C(2′)); 2.48 (*ddd*, *J* = 17.2, 4.8, and 2.7) and 2.61 (*ddd*, *J* = 17.2, 5.2, and 2.7) (2H–C(1″)); 3.70 (*s*, CH_3O–C(1)). MS: 208 (1, M^+), 193 (0,5), 180 (1), 176 (2), 169 (7), 148 (9), 135 (14), 134 (23), 133 (12), 121 (59), 109 (11), 107 (12), 105 (15), 95 (13), *94* (100), 93 (20), 92 (15), 91 (49), 81 (11), 79 (52), 78 (15), 77 (37), 74 (18), 67 (11), 65 (14), 59 (13), 55 (24), 53 (15), 51 (11), 43 (16), 41 (20), 39 (24). Anal. calc. for $C_{12}H_{16}O_3$ (208.25): C 69.21, H 7.74; found: C 69.17, H 7.70.

1.5. *Acetalization of (±)-***17**. A solution of (±)-**17** (47 mg, 0.226 mmol), (2*R*,3*R*)-2,3-butanediol (41 mg, 0.451 mmol), and TsOH·H_2O (5 mg) in benzene (5 ml) was boiled under reflux at a *Dean-Stark* trap for 4 h (Ar). After quenching with sat. $NaHCO_3$-solution, the mixture was worked up with Et_2O. Chromatography (silica gel, hexane/Et_2O 2:1) of the crude product (74 mg) gave 58 mg (91%) of a 1:1 mixture of acetals **20** and **21**, both *ca.* 10:1 mixtures of 7′,6′-*trans*/*cis* epimers, according to GC (*UCON*, 160°, 0.35 kg/cm^2), **20**: t_R = 8.1 min (46.5%) and t_R = 9.5 min (3.3%), **21**: t_R = 8.5 min (46.2%) and t_R = 9.0 min (4.0%).

*Methyl (2′*R*,3′*R*,7′*R*)- and Methyl (2′*R*,3′*R*,7′*S*)-3-[2′,3′-Dimethyl-6′-(2″-propinyl)-1′,4′-dioxaspiro[4.4]non-7′-yl]propionate* (**20**/**21**). IR (CCl_4): 3308*m*, 2970*m*, 2950*m*, 2930*m*, 2870*m*, 2120*w*, 1740*s*, 1452*m*, 1435*m*, 1378*m*, 1375*m*, 1348*w*, 1308*w*, 1288*w*, 1250*m*, 1195*m*, 1155*m*, 1092*m*, 1018*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 1.14–1.32 (*m*, CH_3–C(2′), CH_3–C(3′)); 1.0–2.6 (*m*, 12H); 1.90 (*t*, *J* = 2.5, H–C(3″)); 3.36–3.74 (*m*, H–C(2′), H–C(3′)); 3.63 (*s*, CH_3O–C(1)). MS: 280 (2, M^+), 265 (1), 251 (7), 249 (3), 213 (3), 193 (19), 166 (21), 151 (14), 128 (16), *127* (100), 121 (12), 114 (15), 107 (6), 105 (7), 93 (8), 91 (21), 79 (21), 77 (19), 73 (5), 71 (6), 65 (6), 56 (20), 55 (45), 53 (7), 43 (12), 41 (13), 39 (8). Anal. calc. for $C_{16}H_{24}O_4$ (280.35): C 68.54, H 8.63; found: C 68.44, H 8.76.

2. Cleavage of Dione 1 with Tetra-Alkyl Titanates – 2.1. *Reaction with Ti(OEt)$_4$.* A solution of **1** (108 mg, 0.60 mmol) and $Ti(OEt)_4$ (80 mg, 0.35 mmol) in dry EtOH (5 ml) was boiled for 16 h under reflux (Ar). The cooled mixture was quenched with 1N HCl (3 ml) and worked up with Et_2O. Chromatography (silica gel, hexane/Et_2O 1:1) gave 128 mg (94%) of *ethyl 4-(2′-methyl-3′-oxocyclohexyl)butyrate* ((±)-**5**), mixture of 1′,2′-*cis*/*trans*-epimers, according to GC (*UCON*, 150°, 0.35 kg/cm^2): t_R = 5.2 min (66%, *trans*) and t_R = 5.5 min (44%, *cis*). IR (CCl_4): 2950*m*, 2930*s*, 2860*m*, 1727*s*, 1708*s*, 1445*m*, 1426*w*, 1370*m*, 1343*w*, 1310*m*, 1215*m*, 1176*s*, 1095*m*, 1032*m*, 958*w*, 850*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 1.00 and 1.03* (2*d*, *J* = 6.5, CH_3–C(2′)); 1.24 (*t*, *J* = 7, CH_3CH_2O–C(1)); 0.9–2.7 (*m*, 14H); 4.09 and 4.10* (2*q*, *J* = 7, CH_3CH_2O–C(1)). MS: 226 (3, M^+), 211 (1), 208 (3), 181 (2), 180 (1), 165 (2), 163 (4), 151 (3), 147 (2), 137 (3), 135 (13), 124 (5), 123 (5), *111* (100), 97 (4), 95 (5), 93 (5), 88 (11), 83 (7), 82 (7), 81 (10), 79 (4), 69 (7), 67 (8), 55 (23), 43 (8), 41 (15). Anal. calc. for $C_{13}H_{22}O_3$ (226.31): C 68.99, H 9.80; found: C 68.93, H 9.82.

2.2. *Reaction with Ti(OEt)$_4$/Diethyl Tartrate.* A mixture of $Ti(OEt)_4$ (3.515 g, 15.4 mmol) and diethyl (+)-(*R*,*R*)-tartrate (3.213 g, 15.6 mmol) was stirred for 2 h at r.t. (Ar). A solution of this catalyst (426 mg) and

dione **1** (177 mg, 0.983 mmol) in dry EtOH (5 ml) was boiled under reflux for 6 days (Ar). After cooling and acidification (1N HCl), the mixture was worked up with Et_2O. Chromatography (silica gel, hexane/Et_2O 3:1) gave 182 mg (81%) of **5**, mixture of 1',2'-epimers, *trans/cis* 70:30, according to GC (see *2.1*). $[\alpha]_D = -4.9°$ ($c = 2.09$, $CHCl_3$). Part of this material (65 mg, 0.287 mmol) was stirred for 4 h at r.t. in CH_3ONa/CH_3OH, obtained by adding Na (20 mg, 0.87 mgAt) to 5 ml of CH_3OH. Workup with Et_2O followed by chromatography (silica gel, hexane/Et_2O 2:1) gave 61 mg (quant.) of **3**, mixture of 1',2'-epimers, *trans/cis* 77:23, according to GC (see [9]). $[\alpha]_D = -4.8°$ ($c = 2.175$, $CHCl_3$); 13% excess of (1'*S*)-enantiomer.

3. *Retro-Claisen* Reaction with the Na-Salt 6 of (−)-Ephedrine. – 3.1. *General Procedure.* To a suspension of NaH (407 mg, 55–60% suspension in nujol, 9.3–10.2 mmol) in dry THF (43 ml) (−)-ephedrine (1.699 g, 10.3 mmol), purified by distillation (bulb-to-bulb, 100°/0.1 mm) and dried (h.v./P_2O_5), was added within 1 h. Stirring was continued for 24 h, affording a clear solution of reagent **6**. To a solution of the β-diketone (1 mmol) in THF (1 ml) 5 ml of the reagent solution (1.1–1.2 mmol of **6**) was added within 5 min. The mixture was stirred at a given temperature, untill all of the substrate had been consumed (1–20 h). After quenching with H_2O (1 ml), the reaction was worked up as usual with Et_2O; carboxylic acids were removed by washing with sat. $NaHCO_3$-solution. The crude amide was purified by chromatography (silica gel, Et_2O).

To the amide 10 ml of 2N aq. NaOH/dioxane 2:1 (*v/v*) were added, and this mixture was boiled under reflux for 12–16 h. The cooled reaction mixture was acidified with 1N HCl and worked up with Et_2O. The resulting acid was treated with an excess of ethereal CH_2N_2, the ester purified by chromatography (silica gel, hexane/Et_2O 1:1). The acidified aq. phase was again rendered basic by the addition of 10% KOH and extracted with Et_2O. Bulb-to-bulb distillation of the residue of the org. phases gave recovered (−)-ephedrine in 50–85% yield.

3.2. *Cleavage of Dione* **1** *with Na-Salt* **6**. – 3.2.1. *Reaction at Room Temperature.* Treatment of **1** (182 mg, 1.01 mmol) with 5 ml of the standard-solution of **6** for 2 h at r.t. as described above gave 279 mg (80%) of amides **8** and **9**, mixture of 1',2'-epimers, *trans/cis ca.* 3:1, according to ^{1}H-NMR.

*(1"S,2"R)-*N*-(2"-Hydroxy-1"-methyl-2"-phenylethyl)-*N*-methyl-4-(2'-methyl-3'-oxocyclohexyl)butyramide* (**8/9**). IR ($CHCl_3$): 3595*w*, 3650–3100*w*, 2930*m*, 2865*m*, 1697*s*, 1615*s*, 1447*m*, 1402*m*, 1377*w*, 1310*w*, 1120*w*, 1077*w*, 1040*w*, 958*w*, 883*w*. ^{1}H-NMR (100 MHz, $CDCl_3$): 0.99 and 1.03* (2*d*, $J = 7$, CH_3–C(2')); 1.20 (*d*, $J = 7$, CH_3–C(1")); 0.8–2.5 (*m*, 14H); 2.69* and 2.81 (2*s*, CH_3N); 3.2–4.1 (*br., exchangeable with* D_2O, OH); 3.8–4.9 (*m*, H–C(1"), H–C(2")); 7.1–7.5 (*m*, C_6H_5). MS (*di.*): 346 (0.1, $M^+ + 1$), 328 (0.2), 327 (0.6), 238 (15), 202 (2), 189 (3), 181 (2), 148 (4), 135 (5), 122 (4), 111 (10), 105 (6), 101 (3), 97 (2), 95 (2), 93 (2), 91 (2), 83 (3), 82 (3), 81 (3), 79 (6), 77 (8), 69 (4), 67 (4), *58* (100), 55 (14), 43 (5), 42 (5), 41 (10), 39 (4), 29 (5).

Hydrolysis of **8/9** (273 mg, 0.792 mmol) according to the general procedure, followed by esterification with CH_2N_2 gave 146 mg (87%) of **3**, mixture of 1',2'-epimers, *trans/cis* 75:25, according to GC (see [9]), $[\alpha]_D = +27.6°$ ($c = 2.76$, $CHCl_3$), *ca.* 78% excess of (1'*R*)-enantiomer.

3.2.2. *Reaction at 0°.* Dione **1** (180 mg, 1.00 mmol) was treated with 5 ml of reagent **6** in THF for 4 h at 0° according to the general procedure. Usual workup and purification afforded 254 mg (73%) of amides **8/9**. Hydrolysis of **8/9** (248 mg, 0.72 mmol) and esterification with CH_2N_2 gave 126 mg (82%) of **3**, mixture of 1',2'-epimers, *trans/cis* 75:25, according to GC (see [9]), $[\alpha]_D = +28.5°$ ($c = 2.61$, $CHCl_3$), *ca.* 81% excess of (1'*R*)-enantiomer.

3.2.3. *Reaction at* ca. *−20°.* Reagent **6** in THF (5 ml) was added to a cooled (−20°) solution of **1** (183 mg, 1.017 mmol) in THF (1 ml), and stirring was continued for 20 h at −18° to −20°. Workup and purification according to the general procedure gave 225 mg (64%) of amides **8/9**. Hydrolysis of **8/9** (219 mg, 0.635 mmol) and esterification with CH_2N_2 yielded 113 mg (84%) of **3**, mixture of 1',2'-epimers, *trans/cis* 75:25, according to GC (see [9]), $[\alpha]_D = +30.3°$ ($c = 2.51$, $CHCl_3$), *ca.* 86% excess of (1'*R*)-enantiomer.

3.3. *Cleavage of* trans-*Dione* **7** *with* **6**. – 3.3.1. *Reaction at Room Temperature.* Treatment of **7** (180 mg, 1.00 mmol) with 5 ml of reagent solution (1.1–1.2 mmol of **6**) for 2 h at r.t. according to the general procedure gave 245 mg (71%) of amides **8/9**. Following the general procedure, **8/9** (235 mg, 0.681 mmol) was converted to 125 mg (86%) of **3**, mixture of 1',2'-epimers, *trans/cis* 75:25, according to GC (see [9]), $[\alpha]_D = +15.1°$ ($c = 2.53$, $CHCl_3$), *ca.* 43% excess of (1'*R*)-enantiomer.

3.3.2. *Reaction at 0°.* Reagent **6** in THF (5 ml, 1.1–1.2 mmol) was added to a solution of **7** (179 mg, 0.994 mmol) in THF (1 ml) at 0°. After stirring at 0° for 4 h, usual workup and purification gave 206 mg (60%) of amides **8/9**. According to the general procedure, **8/9** (194 mg, 0.562 mmol) was converted to 104 mg (87%) of **3**, mixture of 1',2'-epimers, *trans/cis* 75:25, according to GC (see [9]), $[\alpha]_D = +15.5°$ ($c = 2.31$, $CHCl_3$), *ca.* 44% excess of (1'*R*)-enantiomer.

3.4. *Cleavage of Dione* **10** *with* **6**. Treatment of **10** (156 mg, 1.026 mmol) with 5 ml of reagent solution (1.1–1.2 mmol of **6**) for 2 h at r.t. (Ar) according to the general procedure afforded 266 mg (81%) of **12/13**.

(1″S,2″R)-N-*(2″-Hydroxy-1″-methyl-2″-phenylethyl)*-N-*methyl-3-(2′-methyl-3′-oxocyclopentyl)propionamide* (**12**/**13**). IR ($CHCl_3$): 3600*w*, 3700–3150*w*, 2960*m*, 2930*m*, 2870*m*, 1728*s*, 1618*s*, 1446*m*, 1402*m*, 1373*m*, 1159*w*, 1116*w*, 1037*w*, 982*w*, 950*w*. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.08 (*d*, J = 6, CH_3–C(2′)); 1.23 (*d*, J = 7, CH_3–C(1″)); 1.0–2.6 (*m*, 11H); 2.77* and 2.85 (2*s*, CH_3N); 3.3–4.2 (*br., exchangeable with* D_2O, OH); 3.5–5.0 (*m*, H–C(1″), H–C(2″)); 7.1–7.5 (*m*, C_6H_5). MS (*di.*): 318 (7, M^+ +1), 300 (6), 211 (22), 210 (71), 202 (10), 153 (9), 148 (17), 118 (15), 107 (10), 101 (19), 91 (8), 79 (18), 77 (17), 69 (10), *58* (100), 55 (31), 43 (11), 42 (18), 41 (20).

Amides **12**/**13** (229 mg, 0.722 mmol) were hydrolyzed and esterified according to the general procedure, affording 86 mg (64%) of **16**, 94:6 mixture of 1′,2′-epimers, according to GC (see *1.2*), $[\alpha]_D = -5.7°$ (c = 2.42, $CHCl_3$). Acetalization of **16** (34 mg, 0.185 mmol) with (2*R*,3*R*)-2,3-butanediol (34 mg, 0.38 mmol) as described above (*1.3*) afforded 45 mg (95%) of **18** and **19**, GC (see *1.3*): **18**, t_R = 6.0 min (41.9%) and t_R = 7.1 min (4.2%); **19**, t_R = 6.3 min (47.6%) and t_R = 6.8 min (6.3%), **18**/**19** *ca.* 46:54 (8% ee).

3.5. *Cleavage of Dione* **11** *with* **6**. Treatment of **11** (178 mg, 1.011 mmol) with 5 ml of reagent solution (1.1–1.2 mmol of **6**) for 1 h at r.t. according to the general procedure gave 237 mg (68%) of **14**/**15**.

(1″S,2″R)-N-*(2″-Hydroxy-1″-methyl-2″-phenylethyl)*-N-*methyl-3-[2′-(2‴-propynyl)-3′-oxocyclopentyl]-propionamide* (**14**/**15**). IR ($CHCl_3$): 3600*w*, 3700–3100*w*, 3300*m*, 2985*m*, 2925*m*, 2870*w*, 2115*w*, 1735*s*, 1620*s*, 1447*m*, 1402*m*, 1376*w*, 1330*w*, 1132*m*, 1080*w*, 1040*w*, 982*w*. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.23 (*d*, J = 7, CH_3–C(1″)); 1.0–2.7 (*m*, 12H); 1.93 (*t*, J = 2.5, H–C(3‴)); 2.76* and 2.83 (2*s*, NCH_3); 3.2–4.1 (*br., exchangeable with* D_2O, OH); 3.5–5.1 (*m*, H–C(1″), H–C(2″)); 7.1–7.5 (*m*, C_6H_5). MS (*di.*): 342 (0.1, M^+ +1), 323 (0.6), 267 (0.5), 266 (0.4), 234 (26), 206 (2), 202 (7), 189 (2), 148 (13), 133 (2), 131 (2), 118 (11), 117 (5), 107 (5), 105 (5), 93 (3), 91 (12), 79 (12), 77 (14), 65 (4), *58* (100), 57 (5), 56 (7), 55 (10), 43 (4), 42 (7), 41 (6), 39 (4).

Hydrolysis (8 h of reaction time) of **14**/**15** (211 mg, 0.618 mmol) and esterification according to the general procedure gave 44 mg (34%) of **17**, 89:11 mixture of 1′,2′-epimers, according to GC (see *1.4*), $[\alpha]_D = -37.7°$ (c = 2.06, $CHCl_3$). Acetalization of **17** (36 mg, 0.173 mmol) with (2*R*,3*R*)-2,3-butanediol (32 mg, 0.356 mmol) as described above (*1.5*) gave 41 mg (84%) of acetals **20** and **21**, GC (see *1.5*): **20**, t_R = 8.1 min (24.5%) and t_R = 9.5 min (1.6%); **21**, t_R = 8.5 min (67.9%) and t_R = 9.0 min (6.0%); **20**/**21** *ca.* 26:74 (48% ee).

4. Cleavage of 1 with *N*-Methylephedrine. (–)-*N*-Methylephedrine (224 mg, 1.25 mmol) dissolved in THF (3 ml) was added to NaH (30 mg, 55–66% suspension in nujol, 0.7–0.75 mmol). After stirring for 3 h at r.t., a solution of **1** (186 mg, 1.033 mmol) in THF (3 ml) was added to the clear reagent solution and stirring at r.t. was continued for 18 h (Ar). The reaction was quenched with AcOH (0.2 ml) and worked up with Et_2O yielding 304 mg of crude esters **22** and **23**. Part of this material (126 mg) was treated for 4 h at r.t. with CH_3ONa/CH_3OH, obtained by reaction of Na (20 mg, 0.87 mg At) with CH_3OH (5 ml). Acidification with 1N HCl, workup with Et_2O, and chromatography (silica gel, hexane/Et_2O 2:1) gave 44 mg (48% based on **1**) of **3**, mixture of 1′,2′-epimers, *trans*/*cis* 78:22, according to GC (see [9]), $[\alpha]_D = +26.1°$ (c = 1.871, $CHCl_3$), *ca.* 75% excess of (1′*R*)-enantiomer. After the addition of KOH the aq. phases were re-extracted with Et_2O, affording 52 mg (81%) of *N*-methylephedrine, $[\alpha]_D = -28°$ (c = 2.13, CH_3OH), corresponds to a purity of 90%.

5. Cleavage of 1 with L-Prolinol. A mixture of NaH (49 mg, 55–60% suspension in nujol, 1.1–1.2 mmol) and L-prolinol (126 mg, 1.248 mmol) in THF (4 ml) was stirred over night at r.t. (Ar). After cooling to 0°, a solution of **1** (189 mg, 1.05 mmol) in THF (1 ml) was added to the suspension within 5 min, and the mixture was stirred for 1 h at 0°. Workup as above (*3.1*) gave 190 mg of crude *(2S)*-N-*[4-(2′-methyl-3′-oxocyclohexyl)butyryl]-2-(hydroxymethyl)pyrrolidine* (**24**/**25**). IR ($CHCl_3$): 3310*w*, 2990*s*, 2960*s*, 2925*s*, 2860*s*, 1700*s*, 1610*s*, 1440*s*, 1374*m*, 1337*m*, 1304*m*, 1132*w*, 1105*w*, 1085*w*, 1071*m*, 1050*m*, 1008*w*, 987*w*, 970*w*, 956*w*.

A solution of **24**/**25** in 6 ml of 1N aq. NaOH/CH_3OH 1:1 (v/v) was boiled for 14 h under reflux. Acidification with 1N HCl, workup with Et_2O, esterification with CH_2N_2, and chromatography (silica gel, hexane/Et_2O 2:1) afforded 111 mg (49%) of **3**, mixture of 1′,2′-epimers, *trans*/*cis* 75:25, according to GC (see [9]), $[\alpha]_D = -13.1°$ (c = 2.36, $CHCl_3$), *ca.* 37% excess of (1′*S*)-enantiomer.

6. Cleavage of 1 with (–)-2-Amino-1-butanol. To a suspension of NaH (49 mg, 55–60% suspension in nujol, 1.1–1.2 mmol) in THF (3 ml) aminobutanol (115 µl, *ca.* 1.22 mmol) was added. After stirring for 3 h at r.t., the suspension was cooled to 0°, and a solution of **1** (178 mg, 0.989 mmol) in 3 ml of THF was added within 5 min. The mixture was stirred for 1 h at 0°, quenched by the addition of H_2O (1 ml) followed by sat. $NaHCO_3$-solution. Workup with Et_2O gave 223 mg of crude *(1″R)*-N-*[1″-(Hydroxymethyl)propyl]-4-(2′-methyl-3′-oxocyclopentyl)butyramide* (**26**/**27**). IR ($CHCl_3$): 3620*w*, 3430*m*, 3680–3100*w*, 2930*s*, 2860*m*, 1698*s*, 1650*s*, 1498*m*, 1455*m*, 1376*w*, 1307*w*, 1133*w*, 1085*w*, 1045*w*, 1010*w*, 960*w*, 890*w*.

Hydrolysis of **26**/**27** (220 mg) and esterification according to the general procedure (*3.1*) yielded 120 mg (57%, based on **1**) of **3**, mixture of 1′,2′-epimers, *trans*/*cis* 75:25, according to GC (see [9]), $[\alpha]_D = +4.1°$ (c = 2.42, $CHCl_3$), *ca.* 11% excess of (1′*R*)-enantiomer.

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