74. Syntheses of (+)- and (−)-Methyl 8-Epinonactate and (+)- and (−)-Methyl Nonactate[1])

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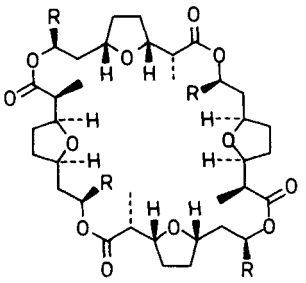
Dedicated to Prof. *Vladimir Prelog* on the occasion of his 81st birthday

(25. II. 87)

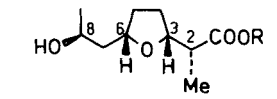
In four synthetic steps, (+)- and (−)-methyl 8-epinonactate ((+)- and (−)-**4**) have been derived from (+)- and (−)-7-oxabicyclo[2.2.1]heptan-2-one ((+)- and (−)-**9**), respectively. The (+)- and (−)-methyl nonactate ((+)- and (−)-**3**) were obtained from (+)- and (−)-**4**, respectively, by *Mitsunobu* displacement reactions. Optical resolution of (±)-**9** *via* chromatographic separation of the corresponding *N*-methyl-*S*-alkyl-*S*-phenylsulfoximides **24** and **25** yielded the starting materials (+)- and (−)-**9**, respectively.

Introduction. – Nonactin (**1**) is the lowest homologue of the actin family of antibiotics [2] which has been isolated from a variety of *Streptomyces* [3]. It is a macrotetrolide composed of two subunits of (−)-nonactic acid ((−)-**2**) and two subunits of (+)-nonactic acid ((+)-**2**), arranged in an alternating order, as determined by *Prelog* and coworkers 25 years ago [4]. Their assignment (S_4 symmetry [5]) was confirmed by crystallographic studies [6].

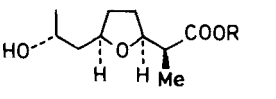
Three syntheses of the natural ionophore **1** have been described. *Gerlach* and coworkers [7a] assembled the linear tetramer from racemic nonactic-acid monomers[3]); macrocyclization of the 2-pyridinethiol ester then gave a mixture of stereoisomeric macrotetrolides, from which **1** could be isolated in 10% yield. In 1975, the first synthesis



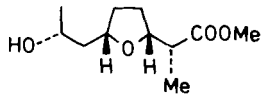
1 R = Me



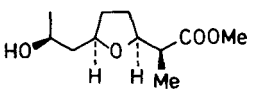
(−)-**2** (2*R*,3*R*,6*S*,8*S*) R = H
(−)-**3** R = Me



(+)-**2** (2*S*,3*S*,6*R*,8*R*) R = H
(+)-**3** R = Me



(−)-**4**



(+)-**4**

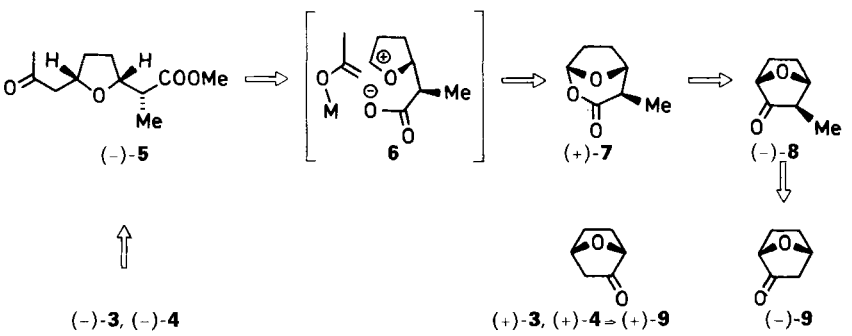
[1]) For a preliminary communication, see [1].
[2]) Part of the Ph. D. thesis of *A. Warm*, Université de Lausanne, 1987.
[3]) For other syntheses of racemic nonactic acid, see [8].

of both enantiomers (−)- and (+)-**2** of nonactic acid was reported by *Schmidt* and coworkers [9]. They also realized the first 'Reverse Coupe du Roi' [5] approach to the synthesis of **1** by coupling the tosylate of (+)-benzyl 8-epinonactate with the potassium salt of (−)-nonactic acid through a S_N2 displacement, to produce a dimer which was then condensed to the tetrameric product **1** in 20% yield [10]. A similar approach to the synthesis of **1** has been presented more recently by *Bartlett* and coworkers [11]. It requires the production of both (+)-nonactic acid ((+)-**2**) and the mesylate of (−)-methyl 8-epinonactate ((−)-**4**) [11].

Already 6 syntheses of (−)-methyl nonactate ((−)-**3**) and (+)-methyl nonactate ((+)-**3**) or of other ester derivatives of **2** have been described. *Schmidt et al.* [9] used (−)-(*S*)-1,2-epoxypropane (derived from ethyl lactate) as starting material for both (−)- and (+)-**3** (separation of diastereoisomers required). *Sun* and *Fraser-Reid* [12] proposed an enantiodivergent approach [13] (5 steps in common) of (−)- and (+)-**3** starting with D-ribose. *Ireland* and *Vevert* [14] obtained a mixture of (−)-**3** and 8-epi isomer (−)-**4** from D-mannose and a mixture of (+)-**3** and (+)-**4** from D-gulono-γ-lactone. *Bartlett* and coworkers [11] described an enantiodivergent synthesis (13 steps in common) of (−)- and (+)-**3** starting with (−)-(*S*)-malic acid. *Page et al.* [15] derived (+)- and (−)-*tert*-butyl 8-*O*-[(*tert*-butyl)dimethylsilyl]nonactates from (*E*)-but-2-enal and but-3-enyl bromide through a technique involving a kinetic resolution of enantiomers. Finally, *Batmangerlich* and *Davidson* [16] prepared (+)- and (−)-*tert*-butyl nonactates and the corresponding 8-epi isomers from L-glutamic acid in 8 steps. All but one of these syntheses required a chiral pool and, in some instances, difficult chromatographic separations. We report here a new and short stereoselective synthesis of (−)- and (+)-methyl 8-epinonactates ((−)- and (+)-**4**). The latter can be transformed to (−)- and (+)-**3**, respectively [8b], by applying the *Mitsunobu* displacement reaction [17]. Our approach employs (−)- and (+)-7-oxabicyclo-[2.2.1]heptan-2-ones, inexpensive starting materials that can readily be prepared in optically pure form. The chiral auxiliaries used to engender asymmetry are recovered at an early stage of the syntheses.

Results and Discussion. – Our retrosynthetic analysis is outlined in *Scheme 1*. Methyl nonactate (**3**) or/and the methyl 8-epinonactate (**4**) will be derived from the corresponding ketone **5**. Reduction of (tetrahydro-2-furyl)propanones have already been reported to be diastereoselective [8b] [12]. Ketone **5** was envisaged as to result from a cross-aldolization-type of reaction involving an equivalent of acetone enolate and zwitterion **6**. The

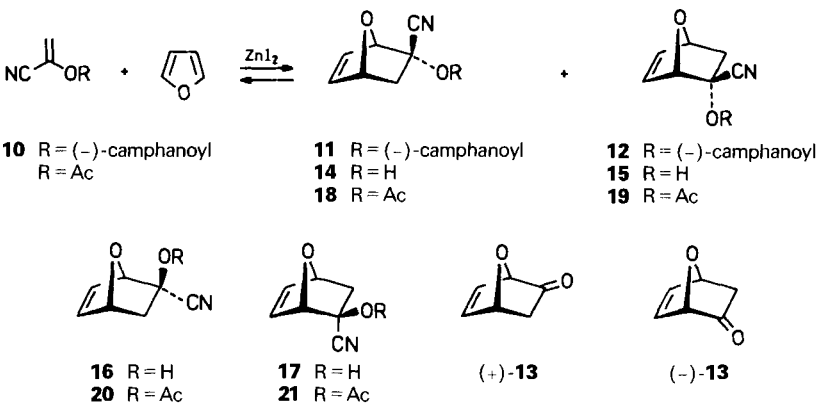
Scheme 1



latter reaction should introduce the C_3 synthon on the same side of the tetrahydrofuran ring as that of the carboxylic group in **6**. The use of a *Lewis* acid (M) capable of double coordination might induce the required stereoselectivity. Zwitterion **6** corresponds to the dissociated form of lactone **7**. Recent work by *Seebach* [18a] and *Johnson* [18b] and coworkers on the condensation of trimethylsilyl enol ether nucleophiles onto related acetals has been our inspiration for that strategy. Lactone **7** will be derived by *Baeyer-Villiger* oxidation of 3-*exo*-methyl-7-oxabicyclo[2.2.1]heptan-2-one (**8**). Peracid oxidation of 7-oxabicyclo[2.2.1]heptan-2-one derivatives are known [19] [20] to be highly regioselective, the O-atom being inserted preferentially between C(1) and C(2) than between C(2) and C(3). Monoalkylation of 7-oxabicyclo[2.2.1]heptan-2-one derivatives at C(3) have been found to be *exo*-face selective [19], thus the obtention of (−)- and (+)-**3** as well as of (−)- and (+)-**4**, will require both enantiomers of 7-oxabicyclo[2.2.1]heptan-2-one ((−)- and (+)-**9**) as starting materials.

Possible precursors of the starting materials (+)- and (−)-**9** are the 7-oxabicyclo-[2.2.1]hept-5-en-2-ones (+)- and (−)-**13** which have already been obtained in optically pure form [21a] [22], their catalytical (Pd/C) hydrogenation giving the corresponding saturated ketones in 96% yield [23].

Scheme 2



10 R = (−)-camphanoyl
R = Ac

11 R = (−)-camphanoyl
14 R = H
18 R = Ac

12 R = (−)-camphanoyl
15 R = H
19 R = Ac

16 R = H
20 R = Ac

17 R = H
21 R = Ac

(+)-**13**

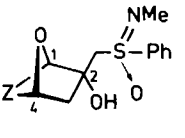
(−)-**13**

In 1983, we reported a first method for the preparation of (+)-**13** [21a] (see *Scheme 2*). ZnI_2-catalyzed *Diels-Alder* addition of furan to (−)-1-cyanovinyl camphanate (**10**, R = camphanoyl), derived from (−)-camphanoyl chloride and 2-oxopropiononitrile, afforded a mixture (92–93%) of 4 diastereoisomeric adducts composed mostly (*ca.* 90%) of **11**/**12** (1:1) from which **11** could be isolated (98% d.e.) in 29% yield. The remaining adducts were recycled nearly quantitively into furan and **10** (R = champhanoyl) on heating in toluene [21a]. Saponification of **11** furnished (+)-**13** (96%) and (−)-camphanic acid, available then to generate more of the optically pure 7-oxanorbornenes **11** and (+)-**13** ('naked sugars', see [19b]). The same method can be applied to prepare (−)-**13** starting with (+)-camphanic acid[4]). Attempts to isolate diastereoisomer **12** from the mother-liquor of the crystallization of **11** allowed one to isolate pure **12** (> 99% d.e. by 360 MHz-^{1}H-NMR [21a]) in low yield only (*ca.* 3%).

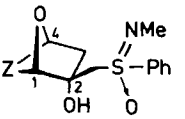
The method reported by *Black et al.* [22] for the preparation of (+)- and (−)-**13** based on the fractional crystallization of the brucine complexes of the cyanhydrines **14**–**17** has now been improved. We obtained **14**–**17** by saponification of the adducts **18**–**21**, resulting

[4]) Both enantiomers of camphanic acid are commercially available, see *e.g.* [21b].

from the *Diels-Alder* addition of furan to 1-cyanovinyl acetate (**10**, R = Ac, *Scheme 2*) [22]. The brucine complex with **16** was easily separated and yielded, after reacetylation, pure **20** in 20% yield (instead of 15% [22]). The latter, upon saponification [22], furnished enone (+)-**13** (> 98% e.e.) nearly quantitatively. From one of the remaining brucine complexes, (−)-**13** was obtained in 80.5% optical purity and 42% yield (see *Exper. Part*). This sample was further enriched by successive crystallizations of the corresponding semicarbazone [24] (prepared in 98% yield) from EtOAc/Et_2O and EtOH followed by treatment with pyruvic acid in AcOH (100°, 2 h). Thus, pure (−)-**13** (3.6%, based on **18**–**21**; > 98% e.e.) was obtained.



22 (1*R*,2*R*,4*R*) Z = CH = CH
24 (1*R*,2*R*,4*S*) Z = CH_2CH_2

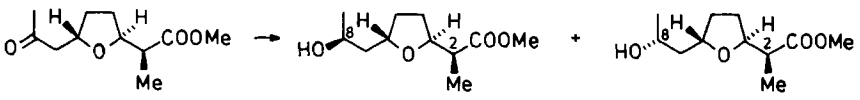


23 Z = CH = CH
25 Z = CH_2CH_2

We have also applied the method of *Johnson* and *Zeller* [25] for the optical resolution of ketones, which is based on the chromatographic separation of *N*-methyl-*S*-alkyl-*S*-phenylsulfoximides. The reaction of (±)-**13** with the conjugate base of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximide [26] gave a 1:1 mixture of **22** and **23** which were obtained in 43.4 and 41.4% yield, respectively, after low-pressure chromatography on silica gel (ΔR_f 0.08). Thermolysis (120°/20 Torr) of **22** and **23** gave (+)- and (−)-**13**, respectively, in low yield (10–15%) due to competitive decomposition. When the same technique was applied directly to (±)-**9**, the sulfoximides **24** (42.2%) and **25** (41.5%) were obtained pure (ΔR_f 0.09). In that case, the thermolysis (180°/15 Torr) of **24** and **25** furnished ketones (+)- and (−)-**9**, respectively, in good yield (96%; 80% based on (±)-**9**) and excellent optical purity (> 99% e.e.).

Monomethylation of (+)-**9** to (+)-**8** was achieved in the following way. KHMDS (prepared from KH and hexamethyldisilizane) in anh. THF was added to a 1:10 mixture of (+)-**9** and MeI (THF, −50°). Workup with 2N HCl and aq. $Na_2S_2O_3$ soln. gave (+)-**8** in 63% yield. In some runs, 10–15% of 3,3-dimethyl-7-oxabicyclo[2.2.1]heptan-2-one was also formed. The latter compound was readily separated from (+)-**8** by medium-pressure chromatography (silica gel). *Baeyer-Villiger* oxidation with 1 equiv. of *m*-chloroperbenzoic acid and $NaHCO_3$ ($CHCl_3$, 12°) gave the unstable oxo acetal (−)-**7** in 94% yield. Addition of 1 equiv. of 2-(trimethylsilyloxy)propene [27] to a 1:1 mixture of (−)-**7** and $TiCl_4$ (CH_2Cl_2, −78°, 3 h) furnished a 1:3 mixture of ketones (+)-**5** and its *trans*-isomer (+)-**26**. The latter was equilibrated into a 4:3 mixture (+)-**5**/(+)-**26** on treatment with 2N KOH (20°, 2 h), acidification, and esterification with CH_2N_2. The isomers (+)-**5**/(+)-**26** were separated by medium-pressure chromatography (silica gel) and were isolated in 36 and 27% yield, respectively. The minor product (+)-**26** could be recycled as above into a 4:3 mixture (+)-**5**/(+)-**26** in 85% yield. These results demonstrated that the condensation of **7** with acetone enolate does not proceed with the stereoselectivity hoped in our retrosynthetic analysis (*Scheme 1*). The fact that a mixture of both possible stereoisomers (**5**, **26**) is formed under conditions of kinetic control suggests the intervention of a S_N1 mechanism alone, or competing with a S_N2 mechanism. Steric effects are

Scheme 3



(+)-**26** **27** (minor) (2*S*,3*S*,6*S*,8*S*) (+)-**28** (major) (2*S*,3*S*,6*S*,8*R*)

probably responsible for the favoured displacement reaction with inversion of configuration at the acetal C-centre (S_N2 mechanism or/and S_N1 mechanism with preferential quenching of the cationic intermediate onto the face *anti* with respect to the carboxylic group).

Reduction of (+)-**5** with *L-Selectride* [8b] (THF, −78°) gave a 10:1 mixture (+)-**4**/(+)-**3**. Column chromatography (silica gel) afforded pure (+)-**4** in 82% yield. Under the same conditions, the reduction of (+)-**26** gave a 1:5 mixture **27**/(+)-**28** (*Scheme 3*). Treatment of (+)-**4** with diethyl azodicarboxylate/triphenylphosphine/benzoic acid, followed by saponification (MeOH, MeONa), yielded (+)-**3** in 85% yield [8b]. The structures of **7**–**9**, (+)-**3**, (+)-**4**, (+)-**5**, (+)-**26**, **27**, and (+)-**28** were given by their elemental analyses and spectral data. Those of (+)-**3**, (+)-**4**, **27**, and (+)-**28** were identical to data reported in [11] [12] [10a] [14] (see *Exper. Part*). The enantiomeric forms (−)-**3** and (−)-**4** can be derived in a similar way from (−)-**9**.

Conclusion. – An expeditious synthesis of (+)-methyl 8-epinonactate ((+)-**4**; 4 steps, 17.5% global yield, 23.8% if (+)-**26** was recycled once into (+)-**5**/(+)-**26** 4:3) and (+)-methyl nonactate ((+)-**3**; 5 steps, 15%) has been realized starting from 7-oxabicyclo-[2.2.1]heptan-2-one ((+)-**9**). The latter compound was readily synthesized in its racemic form from inexpensive starting materials in good yield. Then, the enantiomers (+)- and (−)-**9** were obtained in good yield and with high e.e. by optical resolution *via* chromatographic separation of the corresponding *N*-methyl-*S*-alkyl-*S*-phenyl-sulfoximides **24**, and **25**, allowing the recovery of the chiral auxiliary. Alternatively, separation of the brucine complexes of the *Diels-Alder* adducts **14**–**17** gave the precursors (+)- and (−)-**13** of (+)- and (−)-**9** in good optical purity; (+)- and (−)-**9** can also be derived from the *Diels-Alder* adducts of furan to (−) and (+)-1-cyanovinyl camphanates (**10**) obtained by condensation of 2-oxopropionitrile with (−)- and (+)-camphanoyl chloride, respectively. Monoalkylation of 7-oxabicyclo[2.2.1]heptan-2-one (**9**) with groups larger than the methyl group can be envisioned. Furthermore, condensation (**7**→**5**) of trimethylsilyl ethers of enols derived from ketones homologous to acetone to oxo acetals of type **7** should also be possible, thus making our approach potentially applicable to the synthesis of a variety of derivatives of methyl nonactate and methyl 8-epinonactate. In principle [10c], the latter can be combined to generate natural and non-natural homologues of nonactin. We have also shown [28] that centres C(5) and C(6) in 7-oxabicyclo[2.2.1]heptan-2-one (**9**) can be substituted with high stereo- and regioselectivity. This enables us, in principle, to generate nonactic-acid derivatives substituted at C(4) and C(5) of the tetrahydrofuran ring.

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Experimental Part

1. *General.* See [19b] [28].

2. *(1RS,2SR,4RS)- and (1RS,2RS,4RS)-2-Cyano-7-oxabicyclo[2.2.1]hept-5-ene-2-yl Acetate* (**18**/**19**/and **20**/**21**). A mixture of 1-cyanovinyl acetate (*Fluka*; 55.5 g, 52.4 ml, 0.5 mol), ZnI_2 (48 g, 0.15 mol), and furan (68 g, 72.6 ml, 1 mol) was stirred at 20° under N_2 and in the dark. After 3–4 h, furan (34 g, 0.5 mol) was added and the mixture stirred at 20° for 5 days. The mixture was dissolved in Et_2O (1 l) and H_2O (0.5 l), then sat. aq. NaCl soln. (0.5 l) was added under vigorous stirring. The aq. phase was extracted with Et_2O (100 ml, 5 times) and the combined org. extract washed with 5% aq. $NaHCO_3$ soln. (100 ml, 4 times) and sat. aq. NaCl soln. (100 ml, 4 times). The combined aq. phase was reextracted with Et_2O (100 ml, 3 times) and the combined Et_2O extract dried ($MgSO_4$) and evaporated giving 80.7 g of crude **18**/**19**/**20**/**21** containing *ca.* 20% of unreacted 1-cyanovinyl acetate. The latter was distilled off at 20° 10^{-2} Torr. The residue was filtered through a short column of silica gel (500 g, AcOEt/petroleum ether 1:1). After evaporation, 71.1 g (79%) of (**18** + **19**)/(**20** + **21**) 4:1 was obtained [21a] [22]. Transesterification (MeONa, MeOH) of **18**/**19**/**20**/**21** followed by treatment with formaline yielded *(±)-7-oxabicyclo[2.2.1]hept-5-en-2-one* ((±)-**13**) in 89.5% yield [22].

3. *Optical Resolution of (±)-***13** via *the Separation of (+)-(S)-S-{[(1R,2R,4R)-2-Hydroxy-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methyl}-N-methyl-S-phenylsulfoximide* (**22**) *and (−)-(S)-S-{[(1S,2S,4S)-2-Hydroxy-7-oxabicyclo[2.2.1]hept-5-en-2-yl]methyl}-N-methyl-S-phenylsulfoximide* (**23**). To a soln. of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximide [26] (675 mg, 4 mmol) in anh. THF (10 ml) at −25° under Ar, 1.6M BuLi in THF (2.5 ml, 4 mmol) was added dropwise. The mixture was allowed to warm up to 0° under stirring. After 10 min at 0°, the mixture was cooled to −78°, and a soln. of (±)-**13** (418 mg, 3.8 mmol) in anh. THF (2 ml) was added dropwise. After 1 h at −78°, the reaction was terminated (TLC control (silica gel, AcOEt; UV detection): R_f of **22** 0.75; R_f of **23** 0.67), and the mixture was poured into ice-cold sat. aq. NH_4Cl soln. (20 ml) under vigorous stirring. After extraction with Et_2O (25 ml, 4 times), the combined extract was washed with sat. aq. NaCl soln. (25 ml), dried ($MgSO_4$), and evaporated, and the residue chromatographed (*Lichroprep Si60*, 40–63 μm, *Lobar*, AcOEt/petroleum ether 1:1), yielding first 461 mg (43.4%) of pure **22**, and then 440 mg (41.4%) of pure **23** after recrystallization from Et_2O/petroleum ether 1:3. Heating of **22** in a *Büchi* Kugelrohr oven at 120°, 20 Torr gave a volatile product containing (+)-**13** (10–15% yield). Similarly, **23** afforded (−)-**13** as an impure oil in low yield.

Data of **22**. Colourless crystals, m.p. 117–118° (> 99% d.e. by anal. HPLC (*Du Pont*, SiO_2, 500 × 6.2 mm, petroleum ether/AcOEt, 1:1, 4 ml/min)). $[\alpha]_{589}^{25} = +136.3°$, $[\alpha]_{578}^{25} = +142.3°$ $[\alpha]_{546}^{25} = +164.3°$, $[\alpha]_{436}^{25} = +302.7°$, $[\alpha]_{365}^{25} = +530.1°$ (CH_2Cl_2, $c = 1.11$). UV (dioxane): 272 (935), 265 (1190), 259 (1060), 215 (11200). UV (CH_3CN): 272 (1120), 265 (1300), 259 (1190), 215 (11500). IR (CH_2Cl_2): 3200 (br.), 2980, 1730, 1435, 1230, 1140, 1075, 865. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.90–7.86 (*m*, 2 H); 7.67–7.56 (*m*, 3 H); 7.07 (br. *s*, OH); 6.59 (*dd*, *J* = 5.8, 1.5, H–C(5′)); 6.40 (*dd*, *J* = 5.8, 2.0, H–C(6′)); 4.99 (*dm*, *J* = 5.0, H–C(4′)); 4.40 (*m*, *J* ⩽ 1.5, H–C(1′)); 3.66, 3.37 (2*d*, *J* = 13.5 CH_2–C(2′)); 2.84 (*dd*, *J* = 12.0, 5.0, H_{exo}–C(3′)); 2.61 (*s*, CH_3N); 1.50 (*d*, *J* = 12.0, H_{endo}–C(3′)). CI-MS (NH_3): 280 (100, $M + H^+$); 228 (8), 211 (4), 173 (53), 156 (37), 144 (11), 142 (10), 125 (6), 107 (8). Anal. calc. for $C_{14}H_{17}NO_3S$ (279.35): C 60.19, H 6.13; found: C 60.25, H 6.18.

Data of **23**. Colourless crystals, m.p. 122–124° (> 99% d.e. by anal. HPLC). $[\alpha]_{589}^{25} = -14.6°$, $[\alpha]_{578}^{25} = -15.4°$, $[\alpha]_{547}^{25} = -18.3°$ $[\alpha]_{436}^{25} = -37.2°$, $[\alpha]_{365}^{25} = -71.8°$ (CH_2Cl_2, $c = 1.08$). UV (dioxane): 272 (950), 265 (1175), 259 (1100), 215 (11240). UV (CH_3CN): 272 (1180), 265 (1260), 259 (1180), 215 (11390). IR (CH_2Cl_2): 3200 (br.), 2980, 1435, 1230, 1140, 1075, 865. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.92–7.89 (*m*, 2 H); 7.69–7.58 (*m*, 3 H); 6.55 (*dd*, *J* = 5.8, 1.5, H–C(5′)); 6.53 (*dd*, *J* = 5.8, 2.0, H–C(6′)); 5.41 (*m*, *J* ⩽ 1.5, H–C(1′)); 4.88 (*dm*, *J* = 5.0, H–C(4′)); 3.66, 3.46 (2*d*, *J* = 14.0, CH_2–C(2′)); 2.68 (*s*, CH_3N); 1.69 (*dd*, *J* = 12.0, 5.0, H_{exo}–C(3′)); 1.39 (*d*, *J* = 12.0, H_{endo}–C(3′)). CI-MS (NH_3): 280 (100, $M + H^+$), 228 (10), 211 (7), 173 (61), 156 (80), 144 (15), 142 (16), 125 (13), 107 (16). Anal. calc. for $C_{14}H_{17}NO_3S$ (279.35): C 60.13, H 6.13; found: C 60.01, H 6.06.

4. *7-Oxabicyclo[2.2.1]heptan-2-one* ((±)-**9**). A mixture of (±)-**13** (2.2 g, 20 mmol), MeOH (20 ml) and 10% Pd/C (300 mg) was shaken under H_2 at 20° for 12 h. After filtration through *Celite* (3 g), the solvent was distilled off (*Vigreux* column). The residue was distilled *in vacuo* yielding 2.15 g (96%) of colourless oil, b.p. 68–72°/15 Torr [23].

5. *Optical Resolution of (±)-***9** via *the Separation of (+)-(S)-S-{[(1R,2R,4S)-2-Hydroxy-7-oxabicyclo[2.2.1]hept-2-yl]methyl}-N-methyl-S-phenylsulfoximide* (**24**) *and (+)-(S)-S-{[(1S,2S,4R)-2-Hydroxy-7-oxabicyclo[2.2.1]hept-2-yl]methyl}-N-methyl-S-phenylsulfoximide* (**25**). As in *Exper. 3*, 1.209 g (7.15 mmol) of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximide, 4.5 ml (7.2 mmol) of 1.6M BuLi in THF, and 795 mg (7.1 mmol) of (±)-**9** gave 844 mg (42.2%) of **24**, R_f 0.59 (TLC on silica gel, AcOEt), and 830 mg (41.5%) of **25**, R_f 0.50.

On heating **24** (610 mg, 2.17 mmol) in a *Büchi* 'Kugelrohr' oven to 180°/15 Torr, 232 mg (95.5%) of pure (+)-**9** were obtained in the receiver cooled with dry ice, $[\alpha]_{586}^{25} = +27.4°$, $[\alpha]_{578}^{25} = +28.5°$, $[\alpha]_{546}^{25} = +32.8°$, $[\alpha]_{436}^{25} = +60.8°$, $[\alpha]_{365}^{25} = +104°$ (CH_2Cl_2, $c = 1.45$). Other characteristics were identical to those reported [21] [22].

Similarly, **25** afforded pure (−)-**9**, $[\alpha]_{589}^{25} = -28.7°$, $[\alpha]_{578}^{25} = -30.0°$, $[\alpha]_{546}^{25} = -34.7°$, $[\alpha]_{436}^{25} = -64.9°$, $[\alpha]_{365}^{25} = -110.2°$ (CH_2Cl_2, $c = 1.21$).

Data of **24**. Colourless crystals, m.p. 61–62°, > 99% d.e. by anal. HPLC (*Du Pont*, SiO_2, 500 × 6.2 mm, petroleum ether/AcOEt 1:1; 4 ml/min). $[\alpha]_{589}^{25} = +50.1°$, $[\alpha]_{578}^{25} = +52.0°$, $[\alpha]_{546}^{25} = +60.0°$, $[\alpha]_{436}^{25} = +110.7°$, $[\alpha]_{365}^{25} = +196.5°$ (CH_2Cl_2, $c = 0.89$). UV (dioxane): 270 (1050), 263 (1320), 259 (1185), 219 (10330). UV (CH_3CN): 270 (925), 263 (1185), 259 (1090), 219 (9970). IR (KBr): 3230 (br.), 2960, 1440, 1225, 1145, 1110, 1080, 995, 865, 750. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88–7.85 (*m*, 2 H); 7.67–7.56 (*m*, 3 H); 7.12 (br. *s*, OH); 4.56 (*t*, $J = 5.5$, H–C(4′)); 3.96 (*d*, $J = 5.5$, H–C(1′)); 3.43, 3.36 (2*d*, $J = 13.5$, CH_2–C(2′)); 2.69 (*ddd*, $J = 13.0$, 5.5, 2.5, H_{exo}–C(3′)); 2.63 (*s*, CH_3N); 2.39 (*ddd*, $J = 12.0$, 9.5, 4.5, H_{endo}–C(5′)); 1.8–1.5 (*m*, H_{exo}–C(5′), CH_2(6′)); 1.61 (*d*, $J = 13.0$, H_{endo}–C(3′)). ^{13}C–NMR (90 MHz, $CDCl_3$): 139.0 (*s*); 133.2 (*d*, ^1J(C,H) = 161); 129.6 (*d*, ^1J(C, H) = 163, 2C); 129.0 (*d*, ^1J(C,H) = 164, 2C); 83.0 (*d*, ^1J(C,H) = 156, C(1′)); 78.9 (*d*, ^1J(C,H) = 158, C(4′)); 78.7 (*s*, C(2′)); 64.2 (*t*, ^1J(C,H) = 138, *C*–C(2′)); 43.8 (*t*, ^1J(C,H) = 134, C(3′)); 29.8 (*t*, ^1J(C,H) = 133, C(6′)); 28.8 (*q*, ^1J(C,H) = 138, CH_3N); 22.4 (*t*, ^1J(C,H) = 135, C(5′)). CI-MS (NH_3): 282 (100, $M + H^+$), 173 (28), 156 (15), 146 (5), 144 (4), 107 (6). Anal. calc. for $C_{14}H_{19}NO_3S$ (281.37): C 59.76, H 6.81; found: C 59.85, H 6.89.

Data of **25**. Colourless crystals, m.p. 90–92°, > 99% d.e. by anal. HPLC (*Du Pont*, SiO_2, 500 × 6.2 mm, petroleum ether/AcOEt 1:1, 4 ml/min). UV (dioxane): 270 (1030), 263 (1290), 259 (1170), 219 (9700). UV (CH_3CN): 270 (930), 263 (1200), 259 (1100), 219 (10200). IR (KBr): 3180 (br.), 2960, 2920, 1460, 1440, 1235, 1200, 1150, 1135, 985, 875, 740. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.88–7.85 (*m*, 2 H); 7.66–7.55 (*m*, 3 H); 6.97 (br. *s*, OH); 5.01 (*d*, $J = 5.0$, H–C(1′)); 4.42 (*t*, $J = 5.5$, H–C(4′)); 3.37, 3.36 (2*d*, *AB*, $J = 14.0$, CH_2–C(2′)); 2.63 (*s*, CH_3N); 2.46–2.38 (*m*, H_{endo}–C(6′)); 1.81–1.58 (*m*, H_{exo}–C(3′), CH_2(5′), H_{exo}–C(6′)); 1.46 (*d*, $J = 13.0$, H_{endo}–C(3′)). ^{13}C–NMR (90 MHz, $CDCl_3$): 138.7 (*s*); 133.3 (*d*, ^1J(C,H) = 161); 129.6 (*d*, ^1J(C,H) = 163, 2C); 129.1 (*d*, ^1J(C,H) = 164, 2C); 81.0 (*d*, ^1J(C,H) = 160, C(1′)); 79.2 (*s*, C(2′)); 77.4 (*d*, ^1J(C,H) = 158, C(4′)); 62.7 (*t*, ^1J(C,H) = 139, *C*–C(2′)); 47.1 (*t*, ^1J(C,H) = 133, C(3′)); 30.0 (*t*, ^1J(C,H) = 134, C(6′)); 28.8 (*q*, ^1J(C,H) = 138, CH_3N); 22.8 (*t*, ^1J(C,H) = 136, C(5′)). CI-MS (NH_3): 282 (100, $M + H^+$), 173 (28), 156 (13), 146 (5), 144 (4), 107 (5). $[\alpha]_{589}^{25} = +71.6°$, $[\alpha]_{578}^{25} = +75.3°$, $[\alpha]_{546}^{25} = +87.1°$, $[\alpha]_{436}^{25} = +158.6°$, $[\alpha]_{365}^{25} = +272.7°$ (CH_2Cl_2, $c = 0.97$). Anal. calc. for $C_{14}H_{19}NO_3S$ (281.37): C 59.76, H 6.81; found: C 59.79, H 6.89.

6. *Optical Resolution of (±)-***13** via *Separation of the Brucine Complexes of the Corresponding Cyanohydrines* **14**, **15**, **16**, *and* **17**. A 4:1 mixture (**18** + **19**)/(**20** + **21**) (8.95 g, 50 mmol) was dissolved in MeOH (100 ml) under N_2. After addition of 5.4M MeONa in MeOH (0.25 ml), the soln. was allowed to stand at 20° for 5 h. Under vigourous stirring, brucine (9.86 g, 25 mmol) was added. A precipitate appeared after 5 min. After staying at 20° for 12 h, the precipitate was collected and washed with Et_2O (100 ml). After drying *in vacuo*, one obtained 9.61 g (18.1 mmol, 36.2%) of *Complex A*. The filtrate and Et_2O soln. were united and evaporated, yielding a yellowish solid (*Filtrate A*). The latter was dissolved in MeOH (100 ml), and brucine (9.86 g, 25 mmol) was added under vigorous stirring. After staying at 20° for 12 h, the precipitate was collected, yielding 2.97 g (5.6 mmol, 11.2%) of *Complex B*. The *Filtrate B* was concentrated *in vacuo* to 70 ml and cooled to 0°, yielding a second crop of crystals: 2.81 g (5.3 mmol, 10.8%) of *Complex C*. The *Filtrate C* was evaporated, yielding a yellowish solid: 11.15 g (21.0 mmol, 42%). The optical purity of *Complexes A*, *B*, and *C* and of the residue of *Filtrate C* was determined in the following way. To a soln. of 1.5 g (2.82 mmol) of solid in MeOH (30 ml), 5.4M MeONa in MeOH (0.5 ml) was added. The soln. was allowed to stand at 20° for 2 h. A 40% aq. soln. of formaldehyde (formaline, 1.5 ml) was added. After 30 min at 20°, sat. aq. NaCl soln. (80 ml) was added and the mixture acidified to pH 4 with 2N HCl. The mixture was extracted with CH_2Cl_2 (25 ml, 6 times), and the combined extract dried ($MgSO_4$) and distilled (*Vigreux* column). The residue was purified by column chromatography (silica gel, CH_2Cl_2), yielding 295 mg (93%) of **13** whose optical purity was derived from its $[\alpha]_{589}^{25}$ value (for (+)-**13** with 98% e.e.: $[\alpha]_{589}^{25} = 860°$ (CH_2Cl_2, $c = 2.38$) [21a]). *Complex A*: $[\alpha]_{589}^{25} = +757.3°$, 86% d.e. *Complex B:* $[\alpha]_{589}^{25} = +353.6°$, 40.3% d.e. *Complex C:* $[\alpha]_{589}^{25} = -166.2°$, 19% d.e. Residue of *Filtrat C*: $[\alpha]_{589}^{25} = -706.3°$, 80.5% d.e. ($CH_2Cl_2$, $c = 2.4$).

7. *(+)-(1*R,*2*R,*4*R)-*2*-endo-*Cyano-7-oxabicyclo[2.2.1]hept-5-ene-2*-exo-*yl Acetate* (**20**). *Complex A* of *Exper. 6* (8.1 g, 15.25 mmol; 86% d.e.) was dissolved in $CHCl_3$ (130 ml) at 20° and under N_2. Ac_2O (4.3 g, 42.16 mmol) and then pyridine (3.33 g, 42.16 mmol) were added. After staying at 20° for 24 h in the dark, the soln. was washed with 1N HCl (100 ml, 3 times), then with 5% aq. $NaHCO_3$ soln. (50 ml, twice). After drying ($MgSO_4$) and evaporation, the residue was filtered through a short column of silica gel (AcOEt/petroleum ether 1:1). Crystallization from Et_2O/petroleum ether 1:1 yielded 1.51 g of **20** (55.3%; 20% based on **18**/**19**/**20**/**21**), white crystals, same characteristics as reported for **20** with > 99% e.e. [22].

8. *Semicarbazone of (−)-(1*S,*4*S*)-7-Oxabicyclo[2.2.1]hept-5-en-2-one* (−)-**13**. As described in *Exper. 6*, 11.15 g (21 mmol) of the residue of *Filtrate C* (80.5% d.e.) was transformed into (−)-**13**, yielding 2.15 g (93%) of colourless oil. Thereof, 667 mg (6.06 mmol) were dissolved in EtOH/H_2O 2:1 (15 ml). NaOAc (1.06 g) was added

and the soln. cooled to 0°. Semicarbazide chlorohydrate (1.11 g, 10 mmol) was added. After stirring at 0° for 2 h, the temp. was allowed to reach 20°. After 1 h, the mixture was concentrated *in vacuo* to *ca.* 4 ml, extracted with AcOEt (30 ml, 6 times), the extract dried ($MgSO_4$) and evaporated, yielding 993 mg (98%) of yellowish oil, pure by ^{1}H-NMR and TLC (silica gel, CH_2Cl_2/MeOH 4:1, R_f 0.6). Crystallization from AcOEt/petroleum ether 9:1 afforded 700 mg of semicarbazone, colourless crystals, m.p. 162–166°, $[\alpha]_{589}^{25} = -251.6°$ (CH_2Cl_2, $c = 0.64$). Recrystallization from EtOH (3 ml) yielded 250 mg, m.p. 165–168°, $[\alpha]_{589}^{25} = -186.7°$ (CH_2Cl_2, $c = 0.49$). The mother liquor was concentrated to 1.5 ml, yielding 168 mg (17%; 7% based on **18**/**19**/**20**/**21**) of semicarbazone as colourless, rectangular flakes, m.p. 172–175° (this product was transformed into (–)-**13**, see *Exper. 9*). $[\alpha]_{589}^{25} = -335°$, $[\alpha]_{578}^{25} = -351°$, $[\alpha]_{564}^{25} = -410°$, $[\alpha]_{436}^{25} = -798°$, $[\alpha]_{365}^{25} = -1510°$ (CH_2Cl_2, $c = 0.32$). UV (dioxane): 235 (12100). UV (CH_3CN): 231 (14600). IR (KBr): 3500, 3380, 3220, 1720, 1600, 1505, 1445, 1190, 1120, 1030, 920, 735. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.49 (br. *s*, NH); 6.58 (*dd*, *J* = 5.5, 1.8, H–C(5)); 6.43 (*dd*, *J* = 5.5, 1.8, H–C(6)); 5.28 (*dm*, *J* = 4.5, H–C(4)); 5.04 (br. *s*, H–C(1)); 2.42 (*dd*, *J* = 15.0, 4.5, H_{exo}–C(3)); 2.03 (*d*, *J* = 15.0, H_{endo}–C(3)). ^{13}C-NMR (90 MHz, CD_3OD): 160.5 (*s*, CO); 154.4 (*s*, C(2)); 140.2, 133.9 (*2d*, ^1J(C,H) = 178, C(5), C(6)); 81.5 (*d*, ^1J(C,H) = 169, C(1)); 80.3 (*d*, ^1J(C,H) = 167, C(4)); 30.6 (*t*, ^1J(C,H) = 137, C(3)). CI-MS (NH_3): 185 (51, $M + NH_4^+$); 168 (100, $M + H^+$), 116 (6), 99 (13). Anal. calc. for $C_7H_9N_3O_2$ (167.17): C 50.30, H 5.43; found: C 50.29, H 5.33.

9. *(–)-(1S,4S)-7-Oxabicyclo[2.2.1]hept-5-en-2-one* ((–)-**13**). To a soln. of the semicarbazone of *Exper. 8* (167 mg, 1 mmol) in AcOH (1 ml), pyruvic acid (176 mg, 150 µl, 2 mmol) was added and the mixture heated to 100° for 2 h. After cooling to 20°, H_2O (2 ml) was added and the soln. extracted with Et_2O (5 ml, 3 times). The combined extract was washed with 5% aq. $NaHCO_3$ soln. (5 ml), then with sat. aq. NaCl soln. (5 ml), dried ($MgSO_4$), and evaporated. The residue was purified by filtration through a short column of silica gel (CH_2Cl_2) yielding 60 mg (55%) of (–)-**13** as colourless oil. $[\alpha]_{589}^{25} = -867°$ (CH_2Cl_2, $c = 2.4$; [21a]: $[\alpha]_{589}^{25} = +860°$ (CH_2Cl_2, $c = 2.38$) for (+)-**13** with 98% e.e.)

10. *(+)-(1R,3S,4S)-3-*exo*-Methyl-7-oxabicyclo[2.2.1]heptan-2-one* ((+)-**8**). KH (12 g of 20% suspension in oil, *Fluka*) was washed with anh. pentane (150 ml, 5 times) under Ar. After drying in a flow of dry N_2, one obtained 2.9 g (72.5 mmol) of KH as a white powder. Anh. THF (100 ml) was added. Hexamethyldisilazane (12.1 g, 15.6 ml, 75 mmol) was added dropwise to the vigorously stirred suspension maintained at 0°. After the end of H_2 evolution (10–20 min), the mixture was stirred at 20° under Ar for 12 h. The soln. was filtered under Ar through *Celite* and cooled to –60° [29]. It was then poured slowly to a stirred soln. of (+)-**9** (2.8 g, 25 mmol) and MeI (35.5 g, 15.6 ml, 250 mmol) in anh. THF (80 ml) at –60° under Ar (→precipitation of KI). The reaction was followed by GLC, (*SE-30;* aliquot prepared by treatment with 2N aq. HCl and extraction with Et_2O). The reaction was stopped after *ca.* 20 min at –60° by addition, under stirring, of 2N aq. HCl (20 ml) and then of 10% aq. $Na_2S_2O_3$ soln. (80 ml). When the temp. had reached 0°, the pH was adjusted to 4–5 with 2N aq. HCl. The mixture wax extracted with Et_2O (50 ml, 5 times), the combined extract washed with sat. aq. NaCl soln. (40 ml), dried ($MgSO_4$), and distilled (*Vigreux* column). The residue was filtered through silica gel (Et_2O/petroleum ether 1:1) and purified by prep., medium-pressure chromatography (*Waters*; 400 g SiO_2, 150 ml/min, Et_2O/pentane 2:9), yielding 1.98 g (63%) of colourless oil. IR (CH_2Cl_2): 2960, 2940, 2890, 1765, 1460, 1115, 1090, 985, 925. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.43 (*m*, H–C(1)); 4.28 (*m*, H–C(4)); 1.97 (*q*, *J* = 7.0, H_{endo}–C(3)); 1.94–1.89 (*m*, H_{exo}–C(5), H_{exo}–C(6)); 1.71–1.61 (*m*, H_{endo}–C(5), H_{endo}–C(6)); 1.17 (*d*, *J* = 7.0, CH_3–C(3)). ^{13}C-NMR (90 MHz, $CDCl_3$): 214.4 (*s*, C(2)); 81.7 (*d*, ^1J(C,H) = 160, C(1)); 79.6 (*d*, ^1J(C,H) = 167, C(4)); 48.4 (*d*, ^1J(C,H) = 175, C(3)); 27.9 (*t*, ^1J(C,H) = 135, C(6)); 24.1 (*t*, ^1J(C,H) = 136, C(5)); 13.9 (*q*, ^1J(C,H) = 130, CH_3). MS (70 eV): 126 (17, $M^{+\cdot}$), 98 (37), 83 (33), 70 (61), 55 (100). $[\alpha]_{589}^{25} = +67.8°$, $[\alpha]_{578}^{25} = +71.1°$, $[\alpha]_{546}^{25} = +82.5°$, $[\alpha]_{436}^{25} = +160°$, $[\alpha]_{365}^{25} = +332°$ (CH_2Cl_2, $c = 1.36$). Anal. calc. for $C_7H_{10}O_2$ (126.15): C 66.65, H 7.99; found: C 66.59, H 8.03.

11. *(–)-(1S,4S,)-4-*exo*-Methyl-2,8-dioxabicyclo[3.2.1]octan-3-one* ((–)-**7**). A mixture of (+)-**8** (650 mg, 5.16 mmol), $NaHCO_3$ (1 g), *m*-chloroperbenzoic acid (85%, 1.07 g, 5.27 mmol), and anh. $CHCl_3$ (20 ml) was stirred at 12° for 12 h. After filtration, the soln. was washed with sat. aq. $NaHCO_3$ soln. at –10 to 0° (20 ml, 6 times). After drying ($MgSO_4$, –10°), the solvent was evaporated, yielding 723 mg of a semi-crystalline oil containing *ca.* 95% of (–)-**7** (yield 94%). This unstable product was used directly in the next step. It must be stored at $< -20°$ under Ar. $[\alpha]_{589}^{25} = -64.6°$, $[\alpha]_{578}^{25} = -67.3°$, $[\alpha]_{547}^{25} = -76.9$, $[\alpha]_{436}^{25} = -133°$, $[\alpha]_{365}^{25} = -215°$ (CH_2Cl_2, $c = 0.52$). ^{1}H-NMR (360 MHz, $CDCl_3$): 5.90 (*d*, *J* = 4.0, H–C(1)); 4.47 (*d*, *J* = 7.0, H–C(5)); 2.50 (*q*, *J* = 7.2 H–C(4)); 2.37–2.06 (*m*, CH_2(7), H_{exo}–C(6)); 1.84 (*m*, H_{endo}–(6)); 1.46 (*d*, CH_3–C(4)). MS (70 eV): 142 (3, $M^{+\cdot}$), 98 (22), 83 (28), 69 (75), 55 (100).

12. *(+)-(2S)-Methyl 2-[(2'S,5'R)-2',3',4',5'-Tetrahydro-5'-(2-oxopropyl)-2'-furanyl]propanoate* ((+)-**5**) *and (+)-(2S)-Methyl 2-[(2'S,5'S)-2',3',4',5'-Tetrahydro-5'-(2-oxopropyl)-2'-furanyl]propanoate* ((+)-**26**). A soln.

of (−)-**7** (460 mg, 3.1 mmol) in anh. CH_2Cl_2 (5 ml) was cooled to −78° and anh. $TiCl_4$ (590 mg, 340 µl, 3.1 mmol) was added slowly under Ar. A yellow precipitate was formed. After 5 min, a soln. of 2-(trimethylsilyloxy)propene in anh. CH_2Cl_2 (2 ml) was added dropwise within 5 min under stirring and at −78°. After stirring at −78° for 3 h, H_2O (1.5 ml) was added, the mixture allowed to reach 0°, and 2N aq. KOH added until pH 9 (precipitation of TiO_2). The mixture was stirred at 20° for 12 h, and 2N aq. HCl was added until pH 2. A 1M soln. of CH_2N_2 in Et_2O was added at 0° until persistence of the yellow colour. After standing at 20° for 1 h, the mixture was filtered on *Celite*. The 2 phases were separated. The aq. phase was extracted with Et_2O (20 ml, 3 times), the combined org. phase dried ($MgSO_4$) and evaporated, and the residue filtered through a short column of silica gel (AcOEt/petroleum ether 1:1), yielding a 4:3 mixture (+)-**5**/(+)-**26**. Prep. medium-pressure chromatography on silica gel (*Du Pont*, column 250 × 21.2 mm, 15 ml/min, AcOEt/petroleum ether 7:3) gave first 241 mg (36%) of (+)-**5**, then 182 mg (27%) of (+)-**26**.

When the above procedure was repeated without the treatment with KOH, followed by acidification with HCl and esterification with CH_2N_2, a 1:3 mixture (+)-**5**/(+)-**26** was obtained.

*Data of (+)-***5**. Colourless oil. $[\alpha]_{589}^{25}$ = +16.7°, $[\alpha]_{578}^{25}$ = +17.3°, $[\alpha]_{547}^{25}$ = +19.3°, $[\alpha]_{436}^{25}$ = +27.5° (CH_2Cl_2, c = 1.3). IR (film): 2980, 2955, 2885, 1740, 1710, 1460, 1435, 1380, 1360, 1265, 1200, 1165, 1075. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.24 (*quint.*, J = 6.5, H–C(5')); 4.04 (*ddd*, J = 8.0, 7.0, 6.5, H–C(2')); 3.70 (*s*, CH_3OOC); 2.78 (*dd*, J = 16.0, 6.5, 1 H, CH_2–C(5')); 2.58–2.49 (*m*, H–C(2), 1 H of CH_2–C(5')); 2.17 (*s*, CH_3CO); 2.17–2.07, 1.57–1.47 (2*m*, CH_2–(4')); 2.06–1.92, 1.69–1.60 (2*m*, CH_2(3')); 1.13 (*d*, J = 7.0, CH_3–C(2)). ^{13}C-NMR (90 MHz, $CDCl_3$): 207.1 (*s*, CO); 175.0 (*s*, C(1)); 80.6 (*d*, ^1J(C,H) = 150, C(5')); 75.5 (*d*, ^1J(C,H) = 148, C(2')); 51.5 (*q*, ^1J(C,H) = 147, CH_3OOC); 49.8 (*t*, ^1J(C,H) = 128, CH_2–CO); 45.2 (*d*, ^1J(C,H) = 132, C(2)); 31.1 (*t*, ^1J(C,H) = 132, C(4') or C(3')); 30.7 (*q*, ^1J(C,H) = 128, CH_3–CO); 28.4 (*t*, ^1J(C,H) = 132, C(3') or C(4')); 13.3 (*q*, ^1J(C,H) = 128, CH_3–C(2)). MS (70 eV): 214 (6, $M^{+\cdot}$), 199 (17), 196 (18), 183 (14), 182 (12), 157 (16), 154 (18), 128 (100), 100 (85), 55 (68). Anal. calc. for $C_{11}H_{18}O_4$ (214.259): C 61.66, H 8.47; found: C 61.55, H 8.39.

*Data of (+)-***26**. Colourless oil. $[\alpha]_{589}^{25}$ = 32.7°, $[\alpha]_{578}^{25}$ = +34.2°, $[\alpha]_{547}^{25}$ = +38.8°, $[\alpha]_{436}^{25}$ = +65.4° (CH_2Cl_2, c = 1.21). IR (film): 2980, 2955, 2885, 1740, 1710, 1460, 1435, 1375, 1360, 1265, 1200, 1170, 1075. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.30 (*dddd*, J = 8.0, 6.5, 6.5, 6.0, H–C(5')); 4.11 (*ddd*, J = 8.0, 8.0, 6.5, H–C(2')); 3.66 (*s*, CH_3OOC); 2.74 (*dd*, J = 16.0, 7.0, 1 H of CH_2–C(5')); 2.56–2.46 (*m*, H–C(2), 1 H of CH_2–C(5')); 2.17–2.10 (*m*, 1 H of CH_2(4')); 2.14 (*s*, CH_3CO); 2.07–1.99 (*m*, 1 H of CH_2(3')); 1.65–1.45 (*m*, 1 H of CH_2(3'), 1 H of CH_2(4')); 1.08 (*d*, J = 7.0, CH_3–C(2)). ^{13}C-NMR (90 MHz, $CDCl_3$): 207.2 (*s*, CO); 175.1 (*s*, C(1)); 80.1 (*d*, ^1J(C,H) = 150, C(5')); 75.2 (*d*, ^1J(C,H) = 150, C(2')); 51.5 (*q*, ^1J(C,H) = 147, CH_3OOC); 49.6 (*t*, ^1J(C,H) = 126, CH_2–C(5')); 45.0 (*d*, ^1J(C,H) = 133, C(2)); 32.1 (*t*, ^1J(C,H) = 132, C(3') or C(4')); 30.6 (*q*, ^1J(C,H) = 128, CH_3–CO); 29.3 (*t*, ^1J(C,H) = 133, C(4') or C(3')); 13.0 (*q*, ^1J(C,H) = 130, CH_3–C(2)). MS (70 eV): 214 (7, $M^{+\cdot}$), 199 (18), 196 (19), 183 (12), 182 (14), 157 (19), 154 (18), 128 (100), 101 (82), 55 (59). Anal. calc. for $C_{11}H_{18}O_4$ (214.259): C 61.66, H 8.47; found: C 61.54, H 8.47.

13. *Recycling of (+)-***26** *into (+)-***5**. A mixture of (+)-**26** (150 mg, 0.7 mmol) and 2N aq. KOH (2 ml) was stirred at 20° for 12 h, then 2N aq. HCl was added until pH 2. After cooling to 0°, a 1M soln. of CH_2N_2 in Et_2O was added under vigorous stirring until persistence of the yellow colour. Workup as in *Exper. 12*: 127 mg (85%) of 4:3 mixture (+)-**5**/(+)-**26**.

14. *(+)-Methyl 8-Epinonactate* ((+)-**4**). To a soln. of (+)-**5** (98 mg, 0.46 mmol) in anh. THF (4 ml) at −78°, 1M lithium tri(*sec*-butyl)borohydride in anh. THF (*L-Selectride*; 460 µl, 0.46 mmol) was added under stirring and Ar. After 10 min (TLC monitoring (silica gel, AcOEt/petroleum ether 1:1, detection by vaniline)), 2N aq. HCl (2 ml) was added and the mixture allowed to reach 20°. Et_2O (20 ml) was added, the aq. phase reextracted with Et_2O (10 ml, 4 times), the combined org. phase dried ($MgSO_4$) evaporated, and the oily residue separated by column chromatography (silica gel, AcOEt/petroleum ether 1:1), yielding 81 mg (81.5%) of (+)-**4**, then 8 mg (8%) of (+)-**3** (see [8b]). *Data of* (+)-**4**. Colourless oil. $[\alpha]_{589}^{25}$ = +32.3°, $[\alpha]_{578}^{25}$ = +33.4° $[\alpha]_{547}^{25}$ = +38°, $[\alpha]_{436}^{25}$ = +65.2°, $[\alpha]_{365}^{25}$ = +104° ($CHCl_3$, c = 1.2, *cf.* [14]: $[\alpha]_D^{25}$ = +32.9° ($CHCl_3$, c = 1.07)). IR (film): 3500 (br.), 2980, 1740, 1460, 1435, 1375, 1265, 1200, 1170, 1085. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.13–4.05 (*m*, H–C(8)); 4.04–3.96 (*m*, H–C(3), H–C(6)); 3.70 (*s*, CH_3OOC); 3.20 (br. *s*, OH); 2.56 (*dq*, J = 8.5, 7.0, H–C(2)); 2.09–1.97 (*m*, CH_2(4)); 1.71–1.49 (*m*, CH_2(5), CH_2(7)); 1.17 (*d*, J = 6.2, CH_3–C(8)); 1.13 (*d*, J = 7.0, CH_3–C(2)) (*cf.* data in [11]). ^{13}C-NMR (90 MHz, $CDCl_3$): 175.1 (*s*, C(1)); 81.6 (*d*, ^1J(C,H) = 149, C(6)); 80.2 (*d*, ^1J(C,H) = 146, C(3)); 67.8 (*d*, ^1J(C,H) = 141, C(8)); 51.6 (*q*, ^1J(C,H) = 147, CH_3OOC); 45.3 (*d*, ^1J(C,H) = 130, C(2)); 44.7 (*t*, ^1J(C,H) = 123, C(7)); 31.8, 28.5 (2*t*, ^1J(C,H) = 132, C(4), C(5)); 23.4 (*q*, ^1J(C,H) = 126, C(9)); 13.4 (*q*, ^1J(C,H) = 130, CH_3–C(2)). MS (70 eV): 198 (12, $M^{+\cdot} - H_2O$), 183 (13), 172 (31), 157 (53), 129 (70), 125 (77), 85 (90), 71 (100), 55 (86). Anal. calc. for $C_{11}H_{20}O_4$ (216.275): C 61.09, H 9.32; found: C 60.91, H 9.24.

15. *(+)-Methyl Nonactate* ((+)-**3**). A mixture of (+)-**4** (27 mg, 0.125 mmol), triphenylphosphine (68 mg, 0.26 mmol), and benzoic acid (33 mg, 0.27 mmol) in anh. THF (2 ml) was stirred at 20°. Diethyl azodicarboxylate (44 mg, 0.25 mmol, 39 µl) was added slowly (syringe). After staying at 20° for 12 h, the solvent was evaporated and the residue purified by filtration on *Florisil* (10 g, benzene) giving 37 mg of *methyl 8-O-benzoylnonactate* [8b]. This product was dissolved in anh. MeOH (10 ml) and 30% MeONa soln. in MeOH (0.2 ml). After 18 h at 20°, the soln. was concentrated *in vacuo* to *ca.* 2 ml, H_2O (5 ml) was added, and the mixture acidified with 2N HCl (pH ≈ 5) and extracted with CH_2Cl_2 (5 ml, 3 times). The combined extract was dried ($MgSO_4$) and evaporated, yielding 23 mg (85%; [8b]: 90%) of colourless oil, whose data were consistent with those reported in [11]. $[\alpha]_{589}^{25} = +16.1°$, $[\alpha]_{578}^{25} = +16.8°$, $[\alpha]_{547}^{25} = +18.5°$, $[\alpha]_{436}^{25} = +31.5°$, $[\alpha]_{365}^{25} = +51.6°$ (*cf.* $[\alpha]_D^{20} = +16.2°$ ($CDCl_3$, $c = 2.87$) [10a], $[\alpha]_D^{25} + 13.1°$ ($CHCl_3$, $c = 0.7$) [11], $[\alpha]_D^{25} = +22.1°$ ($CHCl_3$, $c = 0.7$) [14], and $[\alpha]_D^{25} = 16.2°$ ($CHCl_3$) [12]). ^{1}H-NMR (360 MHz, $CDCl_3$): 4.19–4.13 (*m*, H–C(6)); 4.09–4.01 (*m*, H–C(8)); 4.03–3.97 (*m*, H–C(3)); 3.70 (*s*, CH_3OOC); 2.55 (*dq*, *J* = 8.5, 7.0, H–C(2)); 2.08–1.95 (*m*, $CH_2(4)$); 1.77 (*ddd*, *J* = 14.0, 8.0, 4.0, 1 H of $CH_2(7)$); 1.70–1.63 (*m*, $CH_2(5)$, 1 H of $CH_2(7)$); 1.21 (*d*, *J* = 6.3, $CH_3(9)$); 1.13 (*d*, *J* = 7.0, CH_3–C(2)). MS (70 eV): 198 (11), 183 (8), 172 (12), 157 (23), 129 (28), 125 (30), 85 (48), 69 (69), 55 (77), 45 (100).

16. *(2S,3S,6S,8S)-Methyl 6,8-Diepinonactate* (= *(2S)-Methyl 2-[(2'S,5'S)-2',3',4',5'-Tetrahydro-5'-((2S)-2-hydroxypropyl)furan-2'-yl]propanoate;* **27**) *and (+)-(2S,3S,6S,8R)-Methyl 6-Epinonactate* (= *(+)-(2S)-Methyl 2-[(2'S,5'S)-2',3',4',5'-Tetrahydro-5'-((2R)-2-hydroxypropyl)furan-2'-yl]propanoate;* (+)-**28**). A soln. of (+)-**26** (105 mg, 0.49 mmol) in anh. THF (4 ml) was treated with 1M *L-Selectride* in anh. THF (49 µl, 0.49 mmol) and the reaction mixture worked up as described in *Exper. 14:* 76 mg (70%) of (+)-**28** and 15 mg (14%) of **27**. *Data of (+)-***28** (*cf.* [11]). Colourless oil. $[\alpha]_{589}^{25} = +24.7°$, $[\alpha]_{578}^{25} = +26°$, $[\alpha]_{547}^{25} = +29°$, $[\alpha]_{436}^{25} = +45°$, $[\alpha]_{365}^{25} = +64°$ ($CHCl_3$, $c = 0.85$). IR (film): 3500, 2980, 1740, 1460, 1435, 1380, 1265, 1200, 1170, 1080. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.24–4.16 (*m*, H–C(6)); 4.18–4.11 (*m*, H–C(3)); 3.69 (*s*, CH_3OOC); 3.26 (br. *s*, OH); 2.54 (*dq*, *J* = 8.5, 7.0, H–C(2)); 2.17–2.02 (*m*, $CH_2(4)$); 1.79–1.49 (*m*, $CH_2(5)$, $CH_2(7)$); 1.16 (*d*, *J* = 6.2, $CH_3(9)$); 1.12 (*d*, *J* = 7.0, CH_3–C(2)). ^{13}C-NMR (90 MHz, $CDCl_3$): 174.9 (*s*, C(1)); 80.2 (*d*, ^1J(C,H) = 150, C(6)); 79.9 (*d*, ^1J(C,H) = 146, C(3)); 67.9 (*d*, ^1J(C,H) = 142, C(8)); 51.6 (*q*, ^1J(C,H) = 146, CH_3OOC); 45.3 (*d*, ^1J(C,H) = 132, C(2)); 44.1 (*t*, ^1J(C,H) = 125, C(7)); 32.6, 29.3 (2*t*, ^1J(C,H) = 132, C(4), C(5)); 23.3 (*q*, ^1J(C,H) = 126, C(9)); 13.3 (*q*, ^1J(C,H) = 130, CH_3–C(2)). MS (70 eV): 198 (10, $M^{+\cdot} - H_2O$), 183 (3), 172 (14), 157 (21), 129 (42), 125 (34), 85 (53), 71 (85), 55 (95), 45 (100).

Data of **27**. Colourless oil. ^{1}H-NMR (360 MHz, $CDCl_3$): 4.30–4.22 (*m*, H–C(6)); 4.15 (*ddd*, *J* = 8.5, 8.0, 6.5, H–C(3)); 4.08, 4.00 (2 *m*, H–C(8)); 3.70 (*s*, CH_3OOC); 2.72 (br. *s*, OH); 2.56 (*dq*, *J* = 8.5, 7.0, H–C(2)); 2.15–2.00 (*m*, $CH_2(4)$); 1.75–1.56 (*m*, $CH_2(5)$, $CH_2(7)$); 1.21 (*d*, *J* = 6.3, $CH_3(9)$); 1.12 (*d*, *J* = 7.0 CH_3–C(2)). MS (70 eV): 198 (21), 183 (10), 172 (14), 157 (37), 129 (59), 125 (44), 85 (62), 69 (84), 55 (95), 45 (100).

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