Tetrahedron: Asymmetry Vol. 1, No. 10, pp. 729-736, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

New Chiral Auxiliaries and New Optically Pure Ketene Equivalents Derived from Tartaric Acids. Improved Synthesis of (-)-7-Oxabicyclo[2.2.1]hept-5-en-2-one.

by **Jean-Louis Reymond** and **Pierre Vogel***

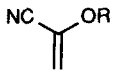
Section de chimie de l'Université, 2, rue de la Barre, CH-1005 Lausanne, Switzerland

(*Received* 22 *August* 1990)

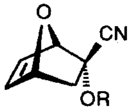
Abstract: Condensation of di-O-acetyl (*R*,*R*)- and (*S*,*S*)-tartaric anhydride with acetals of N-alkylaminoacetaldehyde gave new chiral auxiliaries (1*R*,5*S*,7*R*)- and (1*S*,5*R*,7*S*)-3-alkyl-2-oxo-3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic (RADO(alkyl)-X and SADO(alkyl)-X) derivatives, respectively. The latter could be used to generate the corresponding 1-cyanovinyl esters that add to furan to give readily crystallizable, optically pure *Diels-Alder* adducts. The method was illustrated by application to the synthesis of (-)-(1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one.

Since ketenes do not undergo satisfactory [4+2] cycloadditions because the [2+2] mode is preferred [1], several dienophilic equivalents of ketene have been developed such as 1-cyanovinyl esters [2] [3], 2-chloroacrylonitriles [4], 2-chloroacrylyl chloride [5], 2-aminoacrylonitriles [6], 2-methylthioacrylonitriles [7] and vinyl sulfoxides [8] [9]. In 1983 we showed that (-)-1-cyanovinyl (1'*S*)-camphanate ((-)-**1**) added to furan in the presence of ZnI_2, leading to optically pure adduct (+)-**2** after repetitive recrystallizations; saponification of (+)-**2** gave (+)-**3** and (1*S*)-camphanic acid (recovery of the chiral auxiliary) [10]. The diastereomeric adduct (-)-**5** and the corresponding enone (-)-**3** were obtained as readily from (+)-1-cyanovinyl (1'*R*)-camphanate ((+)-**4**) derived from (1*R*)-camphanic acid. The optically pure 7-oxanorbornenyl derivatives (+)-**2**, (+)-**3** and (-)-**5** ("naked sugars" [11]) are useful chirons [12] in the total synthesis of rare carbohydrates [13], C-nucleosides [14], castanospermine [15] and other compounds of biological interest [16]. Since the scaling up of the preparations of (+)-**2** and (-)-**5** was somewhat troublesome, we have developed a new generation of optically pure 1-cyanovinyl esters derived from inexpensive (*R*,*R*)- and (*S*,*S*)-tartaric acids [17].

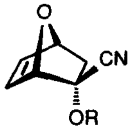
Only one of the two carboxylic groups of tartaric acid is needed to generate the corresponding 1-cyanovinyl ester. The protection of the other carboxylic group and of the two alcoholic functions should resist the highly acidic conditions of the formation of the corresponding acyl chloride required in its condensation with pyruvonitrile into the corresponding ketene equivalent, and of the Lewis acid induced



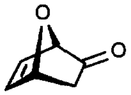
(-)-**1** R=(1*S*)-camphanoyl=R*
(+)-**4** R=(1*S*)-camphanoyl=R'



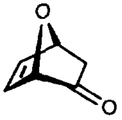
(+)-**2** R=R*



(-)-**5** R=R'

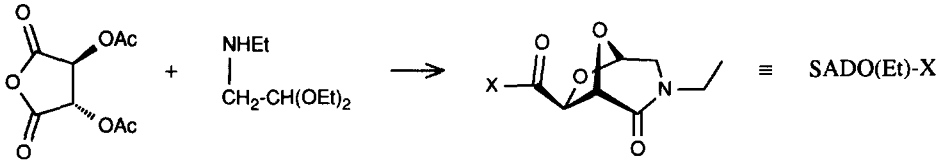


(+)-**3**



(-)-**3**

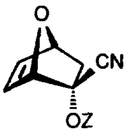
Diels-Alder additions to furan. Furthermore it should allow one to carry out all these transformations, and also the saponification of the adducts into the corresponding enones with recovery of the chiral auxiliary without epimerization at the carbon centres α to the carboxylic groups. These requirements were met for (1*R*,5*S*,7*R*) and (1*S*,5*R*,7*S*)-3-alkyl-2-oxo-3-aza-6,8-dioxabicyclo[3.2.1]octane-7-*exo*-carboxylic (RADO-(alkyl)-X and SADO(alkyl)-X) derivatives obtained by condensation of di-O-acetyl-(*R*,*R*)- and -(*S*,*S*)-tartaric anhydride, respectively, with an acetal of N-alkylaminoacetaldehyde. The bicyclic structure prohibits enolization at the bridgehead centre C(1); epimerization at C(7) can occur but the *exo* stereomers are thermodynamically favoured. The alkyl group at N(3) can be adapted for optimal applications of these new chiral auxiliaries. In the case of the preparation of 7-oxanorbornenyl derivatives ("naked sugars"), adducts derived from RADO(Et)-OH or SADO(Et)-OH were found to have better crystallizability than those derived from RADO(Me)-OH or SADO(Me)-OH. As an illustration, we report here a new synthesis of (-)-**3**.



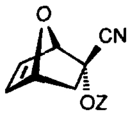
(*S*,*S*)-**6**

7

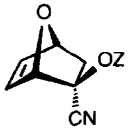
8 X=MeO
9 X=HO
10 X=Cl
11 X=CH_2=C(CN)O



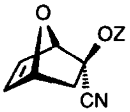
12 Z=SADO(Et)



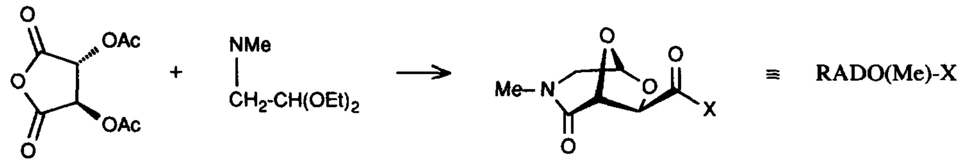
13 Z=SADO(Et)
19 Z=RADO(Me)



14 Z=SADO(Et)



15 Z=SADO(Et)



(*R*,*R*)-**6** **16** **17** X=MeO
18 X=CH_2=C(CN)O

Di-O-acetyl-(*S*,*S*)-tartaric anhydride ((*S*,*S*)-**6**) was reacted with ethylaminoacetaldehyde diethyl acetal (**7**) in CH_2Cl_2. After treatment with MeOH and $SOCl_2$ and then with H_2SO_4/SiO_2, SADO(Et)-OMe (**8**) was obtained (54%). Acidic hydrolysis of **8** gave acid **9** which was transformed into the corresponding acyl chloride **10** with $SOCl_2$ and then condensed with pyruvonitrile (pyridine, CH_2Cl_2) to yield dienophile **11** (86.3%). $ZnBr_2$-induced Diels-Alder addition of **11** to furan (20°C, 7d) gave a mixture of **12** (49%), **13** (31%), **14** +**15** (13%) and unreacted **11** (7%). Two recrystallizations from AcOEt afforded pure **12** in 35% yield (d.e. > 99% by 360 MHz ^{1}H-NMR, $\{^{13}C\}^1$H-satellites vs ^{1}H signals). Pure **13** (17%, d.e. > 99%) could be isolated from the mother-liquors by recrystallizations from AcOEt. When the residue of the mother-liquors of recrystallizations of **12** was heated in toluene (115° C, 12 h), **11** was recovered in 68% yield. Saponification of **12** (NaOH, CH_2O, H_2O, 20°C) gave (-)-**3** (96%) and **9** (78%).

Starting with di-O-acetyl-(*R*,*R*)-tartaric anhydride ((*R*,*R*)-**6**) and methylaminoacetaldehyde diethyl acetal (**16**), the chiral auxiliaries RADO(Me)-X were obtained. The corresponding optically pure ketene equivalent **18** was derived from ester **17**. In the presence of $ZnBr_2$ it added to furan to give a mixture of *Diels-Alder* adducts from which the diastereomer **19** was isolated in 20.6% yield after two recrystallizations from AcOEt.

The *exo* configuration of the cyano group in **12**, **13** (and **19**) was indicated by the difference in chemical shifts of the *exo vs endo* protons at C(3') of the 7-oxanorbornenyl system which amount to ca. 1 ppm, whereas a significantly smaller chemical shift difference is usually observed for *endo*-cyano derivatives [10] [18]. Independent proof was obtained by NOE measurements in their 360 MHz ^{1}H-NMR spectra (e.g.: on irradiating H-C(1) or H-C(7), NOE was observed at H-C(6') of **13**).

The procedure presented here could be readily scaled up. The new chiral auxiliaries RADO(alkyl)-X and SADO(alkyl)-X are inexpensive and available in both enantiomeric forms. Their application to asymmetric synthesis is under exploration in our laboratory.

This work was supported by the *Swiss National Science Foundation, the Fonds Herbette* (Lausanne), and *Hoffmann-La Roche and Co.*, AG (Basel). We thank Mr. Jürgen Wagner for his technical assistance.

Experimental Part.

General. See [19].

N-*Ethylaminoethanol ethyl acetal* (**7**). A mixture of $BrCH_2CH(OEt)_2$ (350 ml), $EtNH_2$ (70% aq, 1 l) MeOH (750 ml) was heated under reflux for 24 h. After addition of NaOH (90 g), the solvent was led off (Vigreux column). Ice (100 g) was added and the mixture extracted with ether (400 ml, 3 times). xtracts were combined and washed with brine (400 ml, twice) and the solvent distilled off (Widmer nn) and the residue distilled and redistilled on CaH_2 : 270 g (74.3%), B.p. 85°C/20 Torr, n_D^{20} = 0.

*Methyl (1S,5*R*,7S)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo-*carboxylate* (SADO--Me: **8**). To a stirred suspension of di-O-acetyl (*S,S*)-tartaric anhydride ((*S,S*)-**6**) (100 g, 0.463 mol) in CH_2Cl_2 (400 ml), **7** (86 ml, 0.463 mol) was added dropwise in 20 min. The mixture was stirred at 20°C h and the solvent evaporated. The residue was dissolved in MeOH (1 l) and $SOCl_2$ (20 ml) was added stirring at 20°C. After 24 h at 20°C, the solvent was evaporated, the residue dried *in vacuo* and lved in toluene (2 l). After addition of acidic SiO_2 (prepared by dropwise addition of conc. H_2SO_4 (20 40 g of silica gel stirred in 500 ml of CH_2Cl_2, and then solvent evaporation), the mixture was heated stirring (oil bath 160°C). Solvents distilling between 85-108°C were distilled off (20 min). After ng to 20°C, the solution was filtered through $NaHCO_3$ (rinsing with CH_2Cl_2) and the solvent rated to dryness. The residue was taken with AcOEt/petroleum ether 3:1 (250 ml) and filtered through gel (200 g; elution with same solvent (1.5 L)). After solvent evaporation, the residue was stallized from Et_2O (400 ml) : 54 g (54%), colourless crystals, m.p. 75-78°C. $[\alpha]^{20}_D = +52.5$, $[\alpha]^{20}_{578}=$, $[\alpha]^{20}_{546} = +61.2$, $[\alpha]^{20}_{436} = +97.0$, $[\alpha]^{20}_{365} = +133.3$ ($c = 10$ g/dm^3, CH_2Cl_2). IR (KBr): 2970, 1750, 1490, 1455, 1435, 1365, 1345, 1330, 1300, 1280, 1210, 1145, 1105, 1080, 1050, 1010, 980, 945, 925, 65, 825, 795, 720, 670. ^{1}H-NMR ($CDCl_3$, 360 MHz): 5.93 (*d*, $^3J = 2.5$, H-C(5)); 4.89 (*s*, H-C(1)); 4.71 C(7)); 3.79 (*s*, MeO); 3.50 (*dd*, $^2J = 12$, $^3J = 3.5$ H_{exo}-C(4)) & 3.22 (*d*, $^2J = 12$, H_{endo}-C(4)); 3.46-3.32 1.13 (*t*, $^3J = 7$, Et). ^{13}C-NMR ($CDCl_3$, 90.55 MHz): 169.2, 165.0 (2*s*), 100.0 (*d*, ^1J(C,H) = 175, C(5)); (*d*, ^1J(C,H) = 155, C(1)); 77.5 (*d*, ^1J(C,H) = 160, C(7)); 52.7 (*q*, ^1J(C,H) = 150, MeO); 50.9 (*t*, ^1J(C,H)), C(4)); 40.0 (*t*, ^1J(C,H) = 140); 11.7 (*q*, Et). MS (70 eV): 216 (8), 215 (72, $M^{+\cdot}$), 170 (15), 156 (20), 16), 114 (12), 113 (12), 99 (15), 86 (16), 85 (13), 71 (32), 59 (18), 58 (100), 57 (30), 56 (15). Anal. for $C_9H_{13}NO_5$ (215.20): C 50.23, H 6.09, N 6.51; found: C 50.30, H 6.01, N 6.43.

*1'-Cyanovinyl ((1S,5*R*,7S)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo-*carboxylate* A soln. of **8** (30 g, 0.14 mol) in H_2O (60 ml) and conc. HCl (3 ml) was heated to 75°C for 3 h. After nt evaporation to dryness (P_4O_{10}), acid **9** (28 g, 100 %) was heated under reflux in $SOCl_2$ (20 ml) until d of gas evolution. $SOCl_2$ was distilled off *in vacuo* and the residue recrystallized from Et_2O (100 ml) etroleum ether (300 ml): 28 g (92%) of **10**. **10** was dissolved in anh. CH_2Cl_2 (120 ml) and pyruvonitrile ml, 0.128 mol). Freshly distilled (over CaH_2) pyridine (10.5 ml) in solution in anh. CH_2Cl_2 (50 ml) dded slowly with stirring at 0°C. The temperature was allowed to reach 20°C in 4 h and the mixture was stirred at 20°C for 20 h. The solvent was evaporated and the residue dissolved in AcOEt (250 ml) and the solution decolourized with active charcoal. After filtration on silica gel (150 g, elution with 600 ml of AcOEt), the solvent was evaporated and the residue recrystallized from AcOEt/Et_2O : 27.7 g (86.3%), colourless crystals, m.p. 90-91.5°C. $[\alpha]^{20}_{D}$ = +53.9, $[\alpha]^{20}_{578}$ = +135.2, (c = 10 g/dm^3, CH_2Cl_2). IR (KBr): 3120, 3035, 2970, 2925, 2865, 2235, 1780, 1660; ^{1}H-NMR ($CDCl_3$, 360 MHz): 5.97 (*d*, ^3J = 2.5); 5.88 & 5.82 (2*d*, ^{2}J = 3.2, $H_2C(2')$); 4.96, 4.86 (2*s*), 3.54 (*dd*, ^{2}J = 12.5, ^3J = 3.5); 3.25 (*d*, ^{2}J = 12.5, $H_2C(4)$); 3.49-3.35 (*m*); 1.15 (*t*, Et). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 165.4 (*s*, CO); 164.2 (*s*, C(2)); 127.0 (*s*, C(1')); 120.1 (*t*, ^1J(C,H) = 170, C(2')); 100.4 (*d*, ^1J(C,H) = 175, C(5)); 77.3 (2*d*, ^1J(C,H) = 165, C(1), C(7)); 50.7 (*t*, ^1J(C,H) = 140, C(4)); 40.1 (*t*, ^1J(C,H) = 140, Et); 11.67 (*q*, ^1J(C,H) = 130, Et). CI-MS (NH_3): 253 (14), 252 ($M^{+\cdot}$,9), 207 (17), 156 (97), 149 (7), 114 (13), 98 (19), 86 (45), 85 (58), 72 (13), 71 (53), 70 (40), 69 (9), 58 (100), 57 (78), 56 (27), 54 (11), 52 (20). Anal. calc. for $C_{11}H_{12}N_2O_5$ (252.22): C 52.38, H 4.80, N 11.11; found: C 52.44, H 4.77, N 11.12.

*(1'S,2'R,4'S)-2'-*exo*-Cyano-7'-oxabicyclo[2.2.1]hept-5'-en-2'-*endo*-yl (1S,5R,7S)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate* (**12**). A mixture of finely ground 4 Å molecular sieves (10 g, dried in a flame under N_2 flow), anh. $ZnBr_2$ (20 g, 89 mmol, finely ground and dried over P_4O_{10}), **11** (20 g, 79.4 mmol) and furan (200 ml) was stirred in the dark at 20°C for 7 d. After distilling off the excess of furan, the residue was taken with CH_2Cl_2 (200 ml), filtered through Celite and washed with H_2O (300 ml, twice). The aq. layer was extracted with CH_2Cl_2 (50 ml, 5 times). The org. extracts were dried ($MgSO_4$) and the solvent evaporated to dryness. The residue was dissolved in boiling AcOEt (150 ml) and the solution was allowed to reach 20°C in 15 h. It was then cooled to 4°C (1 d), and then to -20°C (3 d). The precipitate was washed with Et_2O and recrystallized as above from AcOEt (130 ml) : 8.9 g (35%), colourless crystals, m.p. 147-8°C (dec.). $[\alpha]^{20}_{D}$ = -38, $[\alpha]^{20}_{578}$ = -39.5, $[\alpha]^{20}_{546}$ = -47.3, $[\alpha]^{20}_{436}$ = -97.5, $[\alpha]^{20}{}_{365}$ = -190.6 (c = 10 g/dm^3, CH_2Cl_2). IR (KBr): 2980, 2930, 1770, 1660, 1485, 1430, 1350, 1325, 1300, 1275, 1215, 1195, 1170, 1135, 1105, 1065, 1015, 920, 900, 870, 750, 725, 705. ^{1}H-NMR ($CDCl_3$, 360 MHz): 6.69 (*dd*, ^3J = 6.0, 2.0, H-C(5')); 6.19 (*dd*, ^3J = 6.0, 2.0, H-C(6')); 5.93 (*d*, ^3J = 2.5, H-C(5)); 5.67 (*dd*, ^3J = 2.0, ^{4}J = 1.0, H-C(1')); 5.18 (*ddd*, ^3J = 5.0, 2.0, ^4J = 1.0, H-C(4')); 4.72 (*s*, H-C(1)); 4.68 (*s*, H-C(7)); 3.50 (*dd*, ^2J = 12.5, ^3J = 2.5, H_{exo}-C(4)); 3.22 (*d*, ^2J = 12.5, H_{endo}-C(4)); 3.44-3.33 (*m*, 2 H); 1.14 (*t*, ^3J = 7.0, Et); 2.78 (dd, ^2J = 13.0, ^3J = 5.0, H_{exo}-C(3')); 1.85 (*d*, ^2J = 13.0, H_{endo}-C(3')). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 167.0 (*s*, CO); 164.3 (*s*, C(2)); 140.1 (*d*, ^1J(C,H) = 180, C(5')); 130.4 (*d*, ^1J(C,H) = 175, C(6')); 118.3 (*s*, CN); 100.2 (*d*, ^1J(C,H) = 175, C(5)); 83.4 (*d*, ^1J(C,H) = 175, C(1')); 78.7 (*d*, ^1J(C,H) = 170, C(4')); 77.2 (*d*, C(1)); 77.1 (*d*, C(7)); 72.9 (*s*, C(2')); 50.7 (*t*, ^1J(C,H) = 145, C(4)); 41.0 (*t*, ^1J(C,H) = 145, C(3')); 40.1 (*t*, ^1J(C,H) = 145, Et); 11.6 (*q*, ^1J(C,H) = 130, Et). MS (70 eV): 320 ($M^{+\cdot}$, 4), 207 (15), 179 (7), 157 (8), 156 (45), 114 (8), 99 (6), 98 (8), 92 (5), 86 (26), 81 (7), 71 (34), 70 (7), 69 (12), 68 (100), 65 (8), 58 (54), 57 (40), 56 (16), 54 (9), 53 (7), 52 (15). Anal. calc. for $C_{15}H_{16}N_2O_6$ (320.29): C 56.25, H 5.04, N 8.75; found: C 56.20, H 5.15, N 8.74.

*(1'R,2'S,4'R)-2'-*exo*-Cyano-7'-oxabicyclo[2.2.1]hept-5'-en-2'-*endo*-yl (1S,5R,7S)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate* (**13**). The mother-liquor of the first crystallization of

12 was evaporated to dryness and the residue recrystallized from 20 ml, and then from 14 ml of AcOEt : 4.35 g (17%), colourless crystals, m.p. 139-141°C (dec). $[\alpha]_D^{20}$ = +127.5, $[\alpha]_{578}^{20}$ = +133.1, $[\alpha]_{546}^{20}$ = +152.1, $[\alpha]^{20}{}_{436}$ = +264.2, $[\alpha]^{20}{}_{365}$ = +128.1 (*c* = 10 g/dm^3, CH_2Cl_2). IR (KBr): 3090, 2980, 2940, 2880, 2245, 1770, 1670, 1570, 1490, 1445, 1365, 1325, 1295, 1235, 1205, 1175, 1150, 1110, 1095, 1065, 1045, 1030, 980, 920, 900, 865, 850, 835, 815, 790, 755, 725, 660. ^{1}H-NMR (250 MHz, $CDCl_3$): 6.67 (*dd*, 1 H, ^3J = 5.9, 1.8, H-C(5')); 6.23 (*dd*, 1 H, ^3J = 5.9, 1.8, H-C(6')); 5.91 (*d*, 1 H, ^3J = 2.2, H-C(5)); 5.63 (*dd*, 1 H, ^3J = 1.8, ^5J(1'-4') = 1.0, H-C(1')); 5.17 (*ddd*, 1 H, ^3J = 4.7, 1.8, ^5J(1'-4') = 1.0, H-C(4')); 4.79 (*s*, 1 H, H-C(1)); 4.66 (*s*, 1 H, H-C(7)); 3.50 (*dd*, 1 H, ^2J = 12.3, ^3J = 2.3, H_{exo}-C(4)); 3.37 (*q*, 2 H, ^3J = 7.2, Et); 3.20 (*d*, 1 H, ^2J = 12.3, H_{endo}-C(4)); 2.78 (*dd*, 1 H, ^2J = 12.8, ^3J = 4.7, H_{exo}-C(3')); 1.79 (*d*, 1 H, ^2J = 12.8, H_{endo}-C(3')); 1.13 (*t*, 3 H, ^3J = 7.0, Et). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 167.1 (*s*, CO); 164.4 (*s*, C(2)); 140.0 (*d*, ^1J(C,H) = 180, C(5')); 130.6 (*d*, ^1J(C,H) = 180, C(6')); 118.4 (*s*, CN); 100.2 (*d*, ^1J(C,H) = 175, C(5)); 83.3 (*d*, ^1J(C,H) = 175, C(1')); 78.8 (*d*, ^1J(C,H) = 170, C(4')); 77.2 (*d*, ^1J(C,H) = 170, C(1), C(7)); 73.0 (*s*, C(2')); 50.7 (*t*, ^1J(C,H) = 140, C(4)); 41.1 (*t*, ^1J(C,H) = 145, C(3')); 40.1 (*t*, ^1J(C,H) = 145, Et); 11.7 (*q*, ^1J(C,H) = 130, Et). MS (70 eV): 320 ($M^{+\cdot}$, 3), 209 (6), 207 (13), 206 (3), 179 (5), 157 (6), 156 (50), 114 (6), 98 (10), 86 (25), 85 (29), 72 (11), 71 (29), 69 (9), 68 (100), 58 (61), 57 (34), 56 (13), 54 (9), 52 (12). Anal. calc. for $C_{15}H_{16}N_2O_6$ (320.29): C 56.25, H 5.04, N 8.75; found: C 56.27, H 5.06. N 8.70.

Recovery of **11**. The mother-liquors of the crystallization of **12** were evaporated to dryness, mixed with activated and ground 4 Å molecular sieves and heated under reflux in PhMe (200 ml). After solvent evaporation, the residue was taken with AcOEt, filtered on silica gel. The solvent was evaporated and the residue recrystallized from Et_2O : 6.5 g (32.6%).

(-)-(1S,4S)-7-Oxabicyclo[2.2.1]hept-5-en-2-one ((-)-**3**). A mixture of **12** (10 g, 31.3 mmol), 1N NaOH (40 ml), 40% aq. CH_2O (15 ml, 0.2 mol) was stirred at 20°C for 4 h. Extraction with CH_2Cl_2 (30 ml, 8 times), washing (brine: 70 ml, twice), drying ($MgSO_4$) and distillation gave 3.25 g (95%), oil, b.p. 120°C/20 Torr.[10]

Recovery of *(1S,5R,7S)-3-ethyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic acid* (SADO(Et)-OH, **9**). Acidification of the aq. layer obtained above with conc. HCl (3.5 ml) gave a precipitate : 4.9 g (78%) of **9**, colourless crystals, m.p. 225-227°C (dec.). IR (KBr): 3200-2500, 1740, 1640, 1500, 1455, 1435, 1330, 1280, 1250, 1205, 1150, 1100, 1050, 1020, 930, 905, 870, 825, 765, 710, 665. MS (70 eV): 201 ($M^{+\cdot}$, 10), 156 (13), 112 (11), 86 (11), 71 (35), 70 (14), 58 (100), 57 (41), 56 (23), 55 (12). Anal. calc. for $C_8H_{11}NO_5$ (201.18): C 47.76, H 5.51, N 6.96; found: C 47.77, H 5.52, N 6.99.

*Methyl (1R,5S,7R)-3-methyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylate* (RADO(Me)-OMe, **17**). N-methylaminoethanal dimethylacetal (5 ml, 39 mmol) was added slowly to a soln. of di-O-acetyl (*R,R*)-tartaric anhydride ((*R,R*)-**6**, 8.4 g, 39 mmol) in anh. CH_2Cl_2 (100 ml). After solvent evaporation, MeOH (135 ml) and $SOCl_2$ (2.7 ml) were added. After heating to 50°C for 2 h, the solvent was evaporated and the residue recrystallized from $CHCl_3/Et_2O$/petroleum ether at 20°C. The crystalline product (9.0 g) was dissolved in toluene (180 ml) and acidic silica gel (prepared by slow addition of conc. H_2SO_4

(0.8 g) to stirred silica gel (2.2 g) in CH_2Cl_2, and then solvent evaporation) was added. The mixture was stirred at 160 °C and the vapors were distilled off for 15 min. After cooling to 20 °C, the mixture was filtered through $NaHCO_3$ and the solvent evaporated. The residue was recrystallized from Et_2O at 20 °C, yielding 5.9 g (78%), colourless crystals, m.p. 106 °C. $[\alpha]^{20}_{589}$ = -53.6, $[\alpha]^{20}_{578}$ = -55.3, $[\alpha]^{20}_{546}$ = -62.0, $[\alpha]^{20}{}_{436}$ = -97.6, $[\alpha]^{20}{}_{365}$ = -134 (*c* = 10 g/dm³, CH_2Cl_2). IR (KBr): 3020, 2945, 1750, 1660, 1455, 1430, 1400, 1340, 1285, 1215, 1150, 1100, 1060, 1015, 905, 870, 830, 730, 700, 670. ^1H-NMR (360 MHz, $CDCl_3$): 5.89 (*d*, 1 H, ^3J = 2.3, H-C(5)); 4.90 (*s*, 1 H, H-C(1)); 4.71 (*s*, 1 H, H-C(7)); 3.79 (*s*, 3 H, MeO); 3.49 (*dd*, 1 H, ^2J = 12.2, ^3J = 2.3, H_{exo}-C(4)); 3.22 (*d*, 1 H, ^2J = 12.2, H_{endo}-C(4)); 2.91 (*s*, 3 H, Me). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 169.1 (*s*, CO); 165.5 (*s*, C(2)); 99.8 (*d*, ^1J(C,H) = 175, C(5)); 77.6 (*d*, ^1J(C,H) = 160, C(1)); 77.4 (*d*, ^1J(C,H) = 165, C(7)); 53.7 (*t*, ^1J(C,H) = 140, C(4)); 52.7 (*q*, ^1J(C,H) = 150, OMe); 32.5 (*q*, ^1J(C,H) = 140, Me). MS (70 eV): 202 (3), 201 ($M^{+\cdot}$, 28), 142 (22), 128 (25), 113 (22), 99 (20), 85 (38), 84 (24), 72 (44), 71 (100), 58 (59). Anal. calc. for $C_8H_{11}NO_5$ (201.18): C 47.76, H 5.51, N 6.96; found: C 47.62, H 5.47, N 6.93.

1'-Cyanovinyl ((1R,5S,7R)-3-methyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate) (**18**). 1N NaOH (12 ml) was added in 20 min to a stirred soln. of **17** (2.0 g, 11.3 mmol) in H_2O (10 ml) to 20 °C. After acidification with 2N HCl (6 ml), the solvent was evaporated. $SOCl_2$ (16 ml) was added and the mixture heated under reflux for 1 h. The excess of $SOCl_2$ was distilled off and the residue taken with anh. CH_2Cl_2. The precipitate (NaCl) was filtered off and the solvent evaporated. The residue was recrystallized from CH_2Cl_2/Et_2O/petroleum ether at 20 °C, yielding 1.5 g (73%) of the corresponding acyl chloride. After dissolution in anh. CH_2Cl_2 (10 ml), pyruvonitrile (0.5 ml, 8.3 mmol) was added and the mixture cooled to 0 °C. A soln. of anh. pyridine (0.75 ml) in anh. CH_2Cl_2 (5 ml) was added dropwise under stirring at 0 °C. After stirring at 20 °C for 24 h, the mixture was filtered through a short column of silica gel (EtOAc), yielding 1.15 g (62%), colorless crystals, m.p. 116-117°C after crystallization from Et_2O/petroleum ether (20 °C). $[\alpha]^{20}_{589}$ = -56.6, $[\alpha]^{20}_{578}$ = -58.6, $[\alpha]^{20}_{546}$ = -66.1, $[\alpha]^{20}_{436}$ = -105, $[\alpha]^{20}_{365}$ = -145 (*c* = 10 g/dm³, CH_2Cl_2). IR (KBr): 3120, 3010, 2950, 2930, 1775, 1675, 1630, 1500, 1450, 1405, 1330, 1285, 1230, 1175, 1145, 1100, 1040, 1010, 940, 905, 865. ^1H-NMR (360 MHz, $CDCl_3$): 5.95 (*d*, 1 H, ^3J = 2.3, H-C(5)); 5.86 & 5.81 (2*d*, 2x1 H, ^2J = 3.2, H_2-C(2')); 4.97 (*s*, 1 H, H-C(1)); 4.85 (*s*, 1 H, H-C(7)); 3.55 (*dd*, 1 H, ^2J = 12.0, ^3J = 2.3, H_{exo}-C(4)); 3.26 (*d*, 1 H, ^2J = 12.0, H_{endo}-C(4)); 2.95 (*s*, 3 H, Me). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 165.4 (*s*, CO); 164.6 (*s*, C(2)); 127.0 (*s*, C(1')); 120.1 (*t*, ^1J(C,H) = 165, C(2')); 112.4 (*s*, CN); 100.3 (*d*, ^1J(C,H) = 180, C(5)); 77.2 (*d*, ^1J(C,H) = 165, C(1)); 77.1 (*d*, ^1J(C,H) = 160, C(7)); 53.5 (*t*, ^1J(C,H) = 145, C(4)); 32.26 (*q*, ^1J(C,H) = 140, Me). MS (70 eV): 238 ($M^{+\cdot}$, 7), 193 (14), 142 (88), 137 (10), 99 (7), 91 (16), 86 (14), 85 (77), 84 (27), 72 (75), 71 (100), 69 (18), 58 (85), 52 (53). Anal. calc. for $C_{10}H_{10}N_2O_5$ (238.19): C 50.42, H 4.23, N 11.76; found: C 50.52, H 4.20, N 11.73.

(1'R,2'S,4'R)-2'-exo-Cyano-7'-oxabicyclo[2.2.1]hept-5'-en-2'-endo-yl (1R,5S,7R)-3-methyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate (**19**). A mixture of finely ground 4 Å molecular sieves (6 g, dried in a flame under N_2), anh. $ZnBr_2$ (3.0 g, 13 mmol), **18** (3.0 g, 12.6 mmol), CH_2Cl_2 (3 ml) and furan (30 ml) was stirred at 20 °C in the dark for 7 days. The mixture was filtered through a short

column of silica gel (150 g, AcOEt). The main fraction was recrystallized from AcOEt (200 ml): 1.24 g (32%). A second recrystallization from AcOEt (100 ml) gave 0.8 g (20.6%) pure **19**, colourless crystals, m.p. 175°C (dec.). IR (KBr): 1765, 1665, 1500, 1440, 1400, 1325, 1280, 1215, 1170, 1150, 1105, 1065, 865. ^{1}H-NMR (360 MHz, $CDCl_3$): 6.71 (*dd*, 1 H, ^3J = 6.0, 2.0, H-C(5')); 6.19 (*dd*, 1 H, ^3J = 6.0, 1.5, H-C(6')); 5.92 (*d*, 1 H, ^3J = 2.5, H-C(5)); 5.68 (*dd*, 1 H, ^3J = 2.0, ^4J(H1'-H4') = 1.0, H-C(1')); 5.18 (*ddd*, 1 H, ^3J = 4.5, 1.5, ^4J(H1'-H4') = 1.0, H-C(4')); 4.75 (*s*, 1 H, H-C(1)); 4.71 (*s*, 1 H, H-C(7)); 3.52 (*dd*, 1 H, ^2J = 12.5, ^3J = 2.5, H_{exo}-C(4)); 3.24 (*d*, 1 H, ^2J = 12.5, H_{endo}-C(4)); 2.94 (*s*, 3 H, Me); 2.79 (*dd*, 1 H, ^2J = 13.0, ^3J = 4.5, H_{exo}-C(3')); 1.86 (*d*, 1 H, ^2J = 13.0, H_{endo}-C(3')). ^{13}C-NMR (90.55 MHz, $CDCl_3$): 167.0 (*s*, CO); 164.8 (*s*, C(2)); 140.1 (*d*, ^1J(C,H) = 180, C(5')); 130.4 (*d*, ^1J(C,H) = 180, C(6')); 118.3 (*s*, CN); 100.1 (*d*, ^1J(C,H) = 175, C(5)); 83.4 (*d*, ^1J(C,H) = 175, C(1')); 78.8 (*d*, ^1J(C,H) = 170, C(4')); 77.2 (*d*, ^1J(C,H) = 155, C(1), C(7)); 73.0 (*s*, C(2')); 53.6 (*t*, ^1J(C,H) = 140, C(4)); 41.1 (*t*, ^1J(C,H) = 145, C(3')); 32.6 (*q*, ^1J(C,H) = 140, Me). CI-MS (NH_3): 325 (15), 324 ($M^{+\cdot}$+18, 100), 307 (17), 256 (16), 239 (19), 144 (15), 142 (12), 141 (4), 91 (11). Anal. calc. for $C_{14}H_{14}N_2O_6$ (306.27): C 54.90, H 4.61, N 9.15; found: C 55.19, H 4.56, N 8.85.

REFERENCES

[1] S. Ranganathan, D. Ranganathan, A.K. Mehrotra, *Synthesis* **1977**, 289.

[2] P.D. Bartlett, B.E. Tate, *J. Am. Chem. Soc.* **1956**, *78*, 2473.

[3] A. Oku, H. Hasegawa, H. Shimazu, J. Nishimura, T. Harada, *J. Org. Chem.* **1981**, *46*, 4152; L. Khamliche, A. Robert, *Tetrahedron Lett.* **1986**, *27*, 5491 and ref. cited therein.

[4] H. Krieger, *Suom. Kemstilehti B*, **1963**, *36*, 68; J. Paasivirta, *ibid. A* **1966**, *39*, 120; P.K. Freeman, D.M. Balls, D.J. Brown, *J. Org. Chem.* **1968**, *33*, 2211; E.J. Corey, U. Koelliker, J. Neuffer, *J. Am. Chem. Soc.* **1971**, *93*, 1489 and ref. cited therein.

[5] E.J. Corey, T. Ravindranathan, S. Terashima, *J. Am. Chem. Soc.* **1971**, *93*, 4326 and ref. cited therein.

[6] J.-L. Boucher, L. Stella, *Tetrahedron* **1985**, *41*, 875.

[7] J.-L. Boucher, L. Stella, *Tetrahedron* **1986**, *42*, 3871.

[8] C. Maignan, R.A. Raphael, *Tetrahedron* **1983**, *39*, 3245; R.V. Williams, X. Lin, *J. Chem. Soc., Chem. Commun.* **1989**, 1872 and ref. cited therein.

[9] See also : I. Gupta, P. Yates, *J. Chem. Soc., Chem. Commun.* **1982**, 1227; H.M.R. Hoffmann, K. Giesel, R. Lies, Z.M. Ismail, *Synthesis*, **1986**, 548; W.R. Roush, A.P. Essenfeld, J.S. Warmus, B.B. Brown, *Tetrahedron Lett.* **1989**, *30*, 7305.

[10] E. Vieira, P. Vogel, *Helv. Chim. Acta* **1983**, *66*, 1865; K. A. Black, P. Vogel, *Ibid.* **1984**, *67*, 1612.

[11] A. Warm, P. Vogel, *J. Org. Chem.* **1986**, *51*, 5348; P. Vogel, Y. Auberson, M. Bimwala, E. de Guchteneere, E. Vieira, J. Wagner, in "Trends in Synthetic Carbohydrate Chemistry", ACS Symposium Series 386, Eds. D. Horton, L.D. Hawkins, G.J. McGarvey, American Chemical Society, Washington, D.C., 1989, p. 197.

[12] P. Vogel, D. Fattori, F. Gasparini, C. Le Drian, *Synlett*, **1990**, *1*, 173.

[13] See e.g. Y. Auberson, P. Vogel, *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1498; S. Jeganathan, P. Vogel, *J. Chem. Soc., Chem. Commun.* **1989**, 993.

[14] F. Gasparini, P. Vogel, *J. Org. Chem.* **1990**, *55*; M. Bimwala, P. Vogel, *Helv. Chim. Acta* **1989**, *72*, 1825.

[15] J.-L. Reymond, P. Vogel, *Tetrahedron Lett.* **1989**, *30*, 705.

[16] See e.g. : C. Le Drian, J.-P. Vionnet, P. Vogel, *Helv. Chim. Acta* **1990**, *73*, 161; J. Wagner, P. Vogel, *J. Chem. Soc., Chem. Commun.* **1989**, 1634.

[17] D. Seebach, E. Hungerbühler, in "Modern Synthetic Methods, 1980", Ed. R. Scheffold, Otto Salle Verlag, Frankfurt am Main, 1980, pp. 91-171.

[18] C. LeDrian, P. Vogel, *Helv. Chim. Acta* **1987**, *70*, 1703.

[19] J. Wagner, E. Vieira, P. Vogel, *Helv. Chim. Acta* **1988**, *71*, 624.