Syn-Selective Michael Addition of Amines to Bis-Enones: Synthesis of 1,3,4,7-Tetrasubstituted (4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-2*H*-1,3-diazepin-2-ones†

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O-Protected 1,3,4,7-tetrasubstituted (4*R*,5*S*,6*S*,7*R*)-hexahydro-5,6-dihydroxy-2*H*-1,3-diazepin-2-ones **7a**−**d** are seven-membered cyclic ureas useful as intermediates in the synthesis of HIV-proteinase inhibitors. We succeeded in preparing them using a three-step sequence starting from diethyl isopropylidene-L-tartrate **1**. In a one-pot reaction **1** was transformed via an in situ generated aldehyde and subsequent Wittig reaction into the bis-enones **2a,b**. Treatment with excess of primary amines resulted in a two-fold *syn*-selective Michael addition at low temperature that generated predominantly the C_2-symmetric 1,4-bis(aminoalkyl) derivatives **3a**−**d**. Here we investigated the influence of reaction temperature and configuration of the starting bis-olefin on stereoselectivity. The cyclic ureas **6a**−**d** were formed by treatment of **3a**−**d** with phosgene at elevated temperature. We succeeded in extending this approach to asymmetric substituted cyclic ureas by controlled monoaddition of benzylamine to **2a**, providing the monoaddition product **5a** in good yields. Finally, conjugate addition of a second amine to **5a** followed by cyclization gave the pseudo-C_2-symmetric cyclic urea **9**.

Introduction

The HIV proteinase, which exists as a C_2-symmetric homodimer, is a key enzyme in the life cycle of the human immunodeficiency virus. Thus, the inhibition of this proteinase is an attractive target with potential usefulness for the chemotherapy of the acquired immune deficiency syndrome (AIDS). Identification of 1,3-diazepan-2-ones, cyclic ureas with *RSSR*-configuration, as potent nonpeptidyl inhibitors of HIV-1 proteinase by Du Pont Merck researchers[1] was an important finding in the search for such proteinase inhibitors. Several synthetic routes toward these cyclic ureas have been reported.[2a−c]

Since proteinase inhibitors only suppress the replication of the HIV virus, they would have to be administered every day over a lifetime. Therefore, we aimed at development of inexpensive molecules accessible by short synthetic routes. The possibility of simultaneous manipulation at two sites of the molecule makes the construction of C_2-symmetric compounds very economical. For this reason, as well as the good availability of both enantiomers, we focused on tartaric acid derivatives as starting materials for preparation of C_2-symmetric HIV-1 proteinase inhibitors. Retrosynthetic analysis revealed that such functionalized cyclic ureas with *RSSR*-configuration should be available by two-fold *syn*-selective Michael addition of amines to a bis-enone[3] derived from **1**, followed by cyclization and hydrolysis of the dioxolane ring.

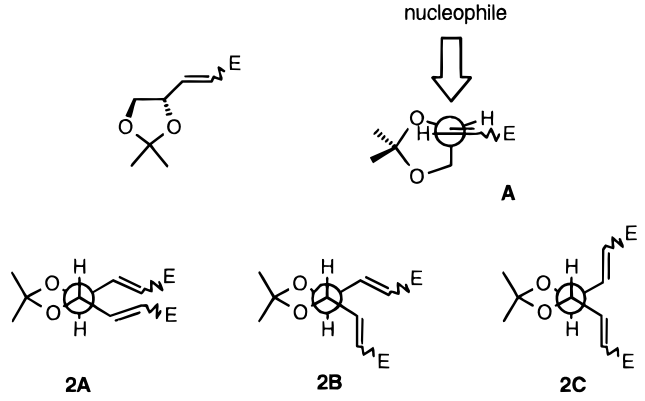

Figure 1.

It has been reported that Michael addition of 1 equiv of benzylamine to **2a** at room temperature in ethanol gives a mixture of *syn* and *anti* addition products with a ratio of 1:3.6.[4] However, high *syn*-selectivity for Michael addition of benzylamine at low temperature under neat conditions,[5] as well as for conjugate addition of lithium enolates[6] and nitromethane[7] to ethyl (*E*)- and (*Z*)-(4*S*)-4,5-isopropylidene-4,5-dihydroxypentenoate is known to occur. This behavior can be rationalized using the modified Felkin-type model **A** (Figure 1) with the hydrogen atom in the inside position, which minimizes the 1,3-allylic strain with the carboalkoxy group in the *Z*-isomer. This situation can be achieved for at least one enone system in conformations **2A** and **2B** without any additional repulsive interactions and should predict high *syn*-selectivity for Michael addition of amines to the tartaric acid derivatives **2a,b**.

† This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

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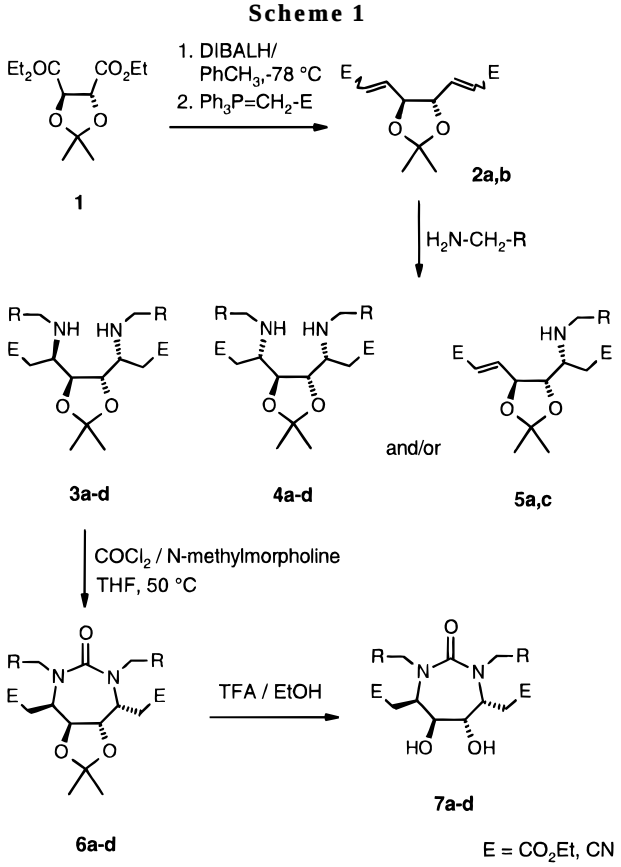
Table 1. Michael Addition of Amines to *E,E*-, *E,Z*-, and/or *Z,Z*-Olefins

entry	olefin	E	R	equiv of amine	temp, °C	time, d	yield (%)[a]	ratio[b] **3**/**4**
1	**2a** *EE*	CO_2Et	Ph	8	−50	28	**3a**, 71; **5a**, 18	5
2	**2a** *EZ*	CO_2Et	Ph	8	−50	28	**3a**, 81; **5a**, 2	7
3	**2a** *ZZ*	CO_2Et	Ph	8	−50	28	**3a**, 83; **5a**, 5	11
4	**2a** mix[c]	CO_2Et	Ph	8	−50	28	**3a**, 81; **5a**, 4	9
5	**2a** mix[c]	CO_2Et	Ph	8	−25	7	**3a**, 80	5
6	**2a** mix[c]	CO_2Et	Ph	8	0	2	**3a**, 70	3
7	**2a** mix[c]	CO_2Et	Ph	8	22	1	**3a**, 61	2
8	**2a** mix[c]	CO_2Et	c-Pr	8	−25	7	**3b**, 84	9
9	**2b** mix[d]	CN	Ph	8	−25	7	**3c**, 75; **5c**, 16	15
10	**2b** mix[d]	CN	c-Pr	8	−25	7	**3d**, 86	18
11	**2a** *EZ*	CO_2Et	Ph	3	−50	28	**3a**, 14; **5a**, 79	6
12	**2a** *ZZ*	CO_2Et	Ph	3	−50	28	**3a**, 26; **5a**, 63	10
13	**2a** mix[c]	CO_2Et	Ph	3	−50	28	**3a**, 15; **5a**, 72	10
14	**2a** mix[c]	CO_2Et	Ph	3	−25	4	**3a**, 17; **5a**, 68	6

[a] Isolated yield. [b] determined by ^{1}H NMR spectroscopy. [c] Mixture of the *E,E*-, *E,Z*-, and *Z,Z*-isomers of **2a** (*E,E*:*E,Z*:*Z,Z* = 3:32:65). [d] Mixture of the *E,E*-, *E,Z*-, and *Z,Z*-isomers of **2b** (*E,E*:*E,Z*:*Z,Z* = 10:62:28).

Scheme 1



Results and Discussion

The realization of our concept started with Wittig olefination of the *in situ* generated dialdehyde by treatment with ylides in a one-pot reaction according to the protocol of Krief et al.[3] The bis-enones **2a,b** were produced as mixtures of their *E,E*-, *E,Z*-, and *Z,Z*-stereoisomers in 91% (**2a**) and 75% (**2b**) yield (Scheme 1). Treatment of these mixtures of isomers with 8 equiv of primary amines under neat conditions[8] produced, as expected, predominantly the desired C_2-symmetric 1,4-diaminoalkyl derivatives **3a**−**d** along with the asymmetric stereoisomers **4a**−**d** and, occasionally, some monoaddition products **5a,c** (Table 1). In addition to an increase of the diastereoselectivity with decreasing reaction temperature (see ref 5) we also observed a clear effect of the configuration of the starting olefin: upon treatment with benzylamine at −50 °C, the best diastereoselectivity was obtained for (*Z,Z*)-**2a** (11:1) followed by (*E,Z*)-**2a** (7:1) and (*E,E*)-**2a** (5:1). A conformation with the allylic hydrogen atom in the inside position is stabilized much more for a *Z*-olefin, minimizing the 1,3-allylic strain with the carboalkoxy group, than for the corresponding *E*-olefin. Therefore, this finding supports the proposed modified Felkin-type model **A**.

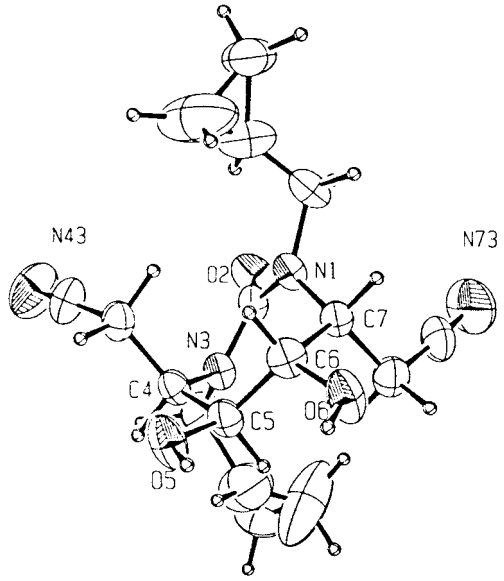


Figure 2. X-ray crystal structure of **7d**.

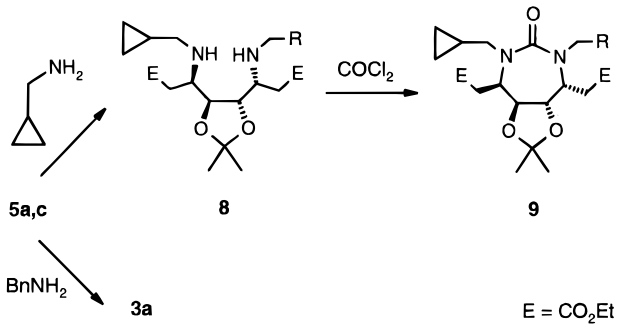
Since a reaction temperature of −50 °C for a period of 28 days is an inacceptable protocol, we performed Michael addition by simple storage of the reaction mixtures in the freezer at a temperature of −30 to −25 °C for one week, to obtain the diamines **3a**−**d** on a multigram scale. The cyclic ureas **6a**−**d**[9] were synthesized in 62−68% yield by simultaneous addition of **3a**−**d** and phosgene or diphosgene to a solution of *N*-methylmorpholine in THF at 50 °C. Finally, the free diols **7a**−**d** were obtained from **6a**−**d** by treatment with trifluoroacetic acid in ethanol. The stereochemical assignment was confirmed by an X-ray structure analysis of **7d** (Figure 2).

In order to expand this approach toward pseudo-C_2-symmetrical *N*-substituted cyclic ureas we also aimed at

(8) Reduction of viscosity of the reaction mixture to allow magnetically stirring at −50 °C was achieved by addition of low amounts of dichloromethane.

(9) **6a,b** were the starting materials for a multitude of HIV-1 protease inhibitors by transformation of the ester group.

Scheme 2



syn-selective monoaddition of amines to the bis-enone **2a** (Scheme 2). This was achieved by treatment of **2a** with 3 equivs of benzylamine at −50 °C. The *E*,*Z*-isomer gave a better yield (79%) than the *Z*,*Z*-isomer (63%). Subsequent reaction of the enone system in **5a** with (aminomethyl)cyclopropane gave the asymmetric substituted bis(aminoalkyl) derivative **8** (82%), which was transformed into the cyclic urea **9** by means of phosgene (67%). Comparison of the ^{1}H NMR data revealed that **5a** is identical with the major isomer assigned as the *anti* isomer in ref 4. To verify that **5a** is indeed the *syn*-product we treated it with benzylamine and again obtained **3a** (93%). This also strongly suggests that 1 equiv of benzylamine reacts with **2a** by *syn*-addition and not by predominant formation of the *anti*-product as reported in ref 4. The structure determination via bi- and tricyclic lactones in ref 4 can neither theoretically nor experimentally be followed due to insufficient documentation (e.g. detailed conditions, yield and ratio of the lactone derivatives). Due to absence of any stereochemical notation of **5a** in the whole manuscript, even a trivial error in imaging cannot be excluded. Finally, missassignment could occur as result of Michael- and retro-Michael reactions in course of the sequence toward these lactones, starting from the unseparable mixture (3.6:1) of **5a** and the minor diastereomer.

Conclusion

A three-step synthesis of seven-membered C_2-symmetric cyclic ureas, starting from diethyl isopropylidene-L-tartrate **1** has been achieved. A two-fold high *syn*-selective Michael addition of primary amines to bis-enones **2a,b**, prepared from **1** by Wittig olefination, was observed, and the dependence of stereoselectivity on reaction temperature and configuration of the starting olefin was investigated. Feasibility of controlled monoaddition of benzylamine to **2a** followed by treatment with a second amine was demonstrated thus expanding the approach to pseudo-C_2-symmetric cyclic ureas.

Experimental Section

Solvents were reagent grade and used without further purification. THF was distilled from potassium/benzophenone. Analytical thin-layer chromatography was performed on 60 F_{254} glass plates (HPTLC, E. Merck). Preparative column chromatography was performed on silica gel (50−63 μm). The chemical shifts are given in units relative to TMS (0 ppm). Elemental analyses were performed by the Analytical Department, Novartis Basle, Switzerland.

X-ray Crystallography. Crystals of **7d** were obtained by spontanous crystallization from EtOAc solution. Tables of crystallographic parameters, atomic coordinates, and bond distances and angles are available from the authors, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ. UK.

General Procedure for Michael Addition of Amines. A mixture of the bis-enones **2a,b** (5.0 mmol) and CH_2Cl_2 (0.5 mL) was cooled to −30 °C, and the amine (40 mmol) was slowly added. Then the reaction mixture was stored at −30 to −25 °C for 7 d. To remove excessive amine, the solution was diluted with Et_2O/cyclohexane (1:3, 20 mL) and filtered over silica gel (30 g) with a gradient (30−70% Et_2O). For preparation of the cyclic ureas we used **3a**−**d** (about 90−95% pure material) without further purification. Pure **3a**−**d** were obtained by column chromatography with the same solvent system.

General Procedure for Formation of the Cyclic Ureas. To a solution of *N*-methylmorpholine (0.85 mL, 7.75 mmol) in dry THF (100 mL) were added the amines **3a**−**d**, **8** (3 mmol) in THF (5 mL), and phosgene (1.93 M in toluene, 1.67 mL) simultanously by two syringe pumps within 24 h at 50 °C. After additional 6 h at 50 °C *N*-methylmorpholine (0.85 mL) and water (1.2 mL) were added, and the mixture was stirred for 2 h. Finally, cyclohexane (100 mL) was added, the precipitate formed was removed by filtration, and the solvent was evaporated. Chromatography on silica gel with Et_2O/cyclohexane (1:2) gave the pure cyclic ureas **6a**−**d** and **9**.

General Procedure for Cleavage of the Isopropylidene Protecting Group. 6a−**d** (0.1 mmol) was dissolved in ethanol (2.0 mL) and treated with TFA (0.1 mL) at rt until no starting material was observed on TLC. After evaporation of the solvent, the residue was redissolved in EtOAc (10 mL) and extracted with saturated $NaHCO_3$ solution (2 mL). The solvent was evaporated and the residue obtained purified by chromatography on silica gel with EtOAc.

(4*S*,5*S*)-1,6-Dicyano-4,5-*O*-isopropylideneocta-2(*Z*),6(*Z*)-dienedinitrile ((*ZZ*)-2b) and (4*S*,5*S*)-4,5-*O*-Isopropylideneocta-2*E*,6*Z*-dienedinitrile ((*EZ*)-2b). The title compounds were prepared according to the procedure described in reference 3. Instead of the $Ph_3P{=}CHCO_2Et$ we used $Ph_3P{=}CHCN$ in ethanol. A 6.48 g amount (30 mmol) of **1** gave 2.81 g (46%) of (*ZZ*)-**2b** and 1.76 g (29%) of (*EZ*)-**2b**. **(*ZZ*)-2b:** mp 94 °C; $[\alpha]^{20}_D$ +362.8° ($CHCl_3$, *c* = 1.15); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 6.55 (m, 2 H); 5.61 (d, *J* = 11.2 Hz, 2 H); 4.67 (m, 2 H); 1.50 (s, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 147.9, 114.3, 112.1, 103.8, 78.3, 26.5. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.48; H, 5.88; N, 13.76. **(*EZ*)-2b:** $[\alpha]^{20}_D$ +96.3° ($CHCl_3$, c = 1.20); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 6.55 (dd, *J* = 16.1 and 4.8 Hz, 1 H); 6.46 (dd, *J* = 11.2 and 8.2 Hz, 1 H); 5.78 (dd, *J* = 16.1 and 1.7 Hz, 1 H); 5.62 (dd, *J* = 11.2 and 1.0 Hz, 1 H); 4.63 (ddd, *J* = 8.2, 8.2 and 1.0 Hz, 1 H); 4.30 (ddd, *J* = 8.2, 4.8 and 1.7 Hz, 1 H); 1.48 (s, 3 H); 1.46 (s, 3 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 148.1, 147.8, 116.3, 114.5, 112.2, 103.9, 102.6, 79.4, 78.6, 26.8, 26.7. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.56; H, 5.83; N, 13.64.

Diethyl (2*R*,3*S*,4*S*,5*R*)-3,4-*O*-isopropylidene-2,5-bis-[(phenylmethyl)amino]-1,6-hexanedicarboxylate (3a): $[\alpha]^{20}_D$ −31.5° ($CHCl_3$, *c* = 1.51); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.34−7.17 (m, 10 H); 4.16 (bs, 2 H); 4.12 (q, *J* = 7.1 Hz, 4 H); 3.89 and 3.73 (AB, *J* = 13.1Hz, 4 H); 3.19 (bt, *J* = 6.4 Hz, 2 H); 2.56 (ABX, 4 H); 1.65 (bs, 2 H); 1.34 (s, 6 H); 1.24 (t, *J* = 7.1 Hz, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 172.3, 140.6, 128.4, 128.2, 127.1, 79.1, 60.4, 54.7, 51.6, 36.9, 27.4, 14.4. Anal. Calcd for $C_{29}H_{40}N_2O_6$: C, 67.95; H, 7.86; N, 5.46. Found: C, 67.90; H, 7.76; N, 5.46.

Diethyl (2*R*,3*S*,4*S*,5*R*)-2,5-bis[(cyclopropylmethyl)amino]-3,4-*O*-isopropylidene-1,6-hexanedicarboxylate (3b): $[\alpha]^{20}_D$ −30.2° ($CHCl_3$, *c* = 1.11); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 4.12 (q, *J* = 7.1 Hz, 4 H); 4.08 (dd, *J* = 2.1 and 1.4 Hz, 2 H); 3.16 (dddd, *J* = 6.0, 6.0, 2.1 and 1.4 Hz, 2 H); 2.30 (m, 8 H); 1.59 (bs, 2 H); 1.37 (s, 6 H); 1.24 (t, *J* = 7.1 Hz, 6 H); 0.88 (m, 2 H); 0.43 (m, 4 H); 0.09 (m, 4 H). Anal. Calcd for $C_{23}H_{40}N_2O_6$: C, 62.70; H, 9.15; N, 6.36. Found: C, 62.59; H, 9.04; N, 6.33.

(3*R*,4*S*,5*S*,6*R*)-4,5-*O*-Isopropylidene-3,6-bis[(phenylmethyl)amino]octanedinitrile (3c): $[\alpha]^{20}_D$ −58.9° ($CHCl_3$, *c* = 1.26); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.39−7.21 (m, 10 H); 4.26 (bs, 2 H); 3.98 and 3.73 (AB, *J* = 13.3 Hz, 4 H); 2.80

(bdd, J = 7.6 and 5.0 Hz, 2 H); 2.64 and 2.51 (ABX, J_{AB} = 16.6 Hz, J_{AX} = 5.0 Hz, J_{BX} = 7.6 Hz, 4 H); 1.66 (bs, 2 H); 1.38 (s, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 139.3, 128.6, 128.2, 127.4, 118.0, 109.5, 78.0, 52.7, 51.0, 27.1, 20.5. Anal. Calcd for $C_{25}H_{30}N_4O_2$: C, 71.74; H, 7.22; N, 13.39. Found: C, 71.45; H, 7.15; N, 13.25.

(3*R*,4*S*,5*S*,6*R*)-3,6-Bis[(cyclopropylmethyl)amino]-4,5-*O*-isopropylideneoctanedinitrile (3d): $[\alpha]^{20}_D$ −57.7° ($CHCl_3$, c = 2.00); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 4.23 (dd, J = 1.3 and 1.2 Hz, 2 H); 3.16 (dddd, J = 7.6, 5.0, 1.3 and 1.2 Hz, 2 H); 2.58 (m, 8 H); 1.45 (bs, 2 H); 1.41 (s, 6 H); 0.92 (m, 2 H); 0.49 (m, 4 H); 0.13 (m, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 118.0, 109.5, 78.1, 54.4, 52.3, 27.1, 20.5, 11.3, 3.4, 3.1. Anal. Calcd for $C_{19}H_{30}N_4O_2$: C, 65.87; H, 8.73; N, 16.17. Found: C, 65.94; H, 8.66; N, 15.94.

Diethyl (2*R*,3*S*,4*S*,5*S*)-3,4-*O*-isopropylidene-2,5-bis-[(phenylmethyl)amino]-1,6-hexanedicarboxylate (4a): $[\alpha]^{20}_D$ −181.6° ($CHCl_3$, c = 0.98); ^{1}H-NMR (500 MHz; $CDCl_3$): δ = 7.31−7.17 (m, 10 H); 4.12 (m, 5 H); 3.91 and 3.72 (AB, J = 13.1 Hz, 2 H); 3.77 and 3.71 (AB, J = 13.0 Hz, 2 H); 3.29 (dt, J = 6.4 and 3.3 Hz, 1 H); 3.09 (dt, J = 6.8 and 4,9 Hz, 1 H); 2.63−2.50 (2 ABX, 4 H); 1.64 (bs, 2 H); 1.36 (s, 3 H); 1.31 (s, 3 H); 1.24 (t, J = 7.1 Hz, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 172.3, 172.2, 140.4, 140.1, 128.2, 128.1, 128.0, 126.8, 108.6, 82,0, 78.2, 60.4, 60.3, 56.9, 54.4, 51.3, 51.0, 37.1, 35.7, 27.2, 27.1, 14.1. Anal. Calcd for $C_{29}H_{40}N_2O_6$: C, 67.95; H, 7.86; N, 5.46. Found: C, 67.98; H, 8.03; N, 5.40.

(4*S*,5*S*,6*R*)-4,5-*O*-isopropylidene-6-[(phenylmethyl)amino]oct-2(*E*)-enedinitrile (5c). Treatment of **2b** (400 mg, 1.96 mmol) with benzylamine (0.64 mL, 5.88 mmol) according the general procedure gave 445 mg (73%) of **5c**. $[\alpha]^{20}_D$ −81.7° ($CHCl_3$, c = 0.60); ^{1}H-NMR (500 MHz; $CDCl_3$): δ = 7.38−7.29 (m, 5 H); 6.50 (dd, J = 16.2 and 5.3 Hz, 1 H); 5.41 (dd, J = 16.2 and 1.7 Hz, 1 H); 4.67 (ddd, J = 5.3, 2.4 and 1.7 Hz, 1 H); 4.05 and 3.77 (AB, J = 13.3 Hz, 2 H); 3.85 (dd, J = 8.2 and 2.4 Hz, 1 H); 2.92 (ddd, J = 8.3, 7.9 and 5.0 Hz, 2 H); 2.73 and 2.59 (ABX, J_{AB} = 16.7 Hz, J_{AX} = 5.0 Hz, J_{BX} = 7.9 Hz, 2 H); 1.69 (bs, 1 H); 1.43 (s, 3 H) 1.39 (s, 3 H). ^{13}C-NMR (125.8 MHz; $CDCl_3$): δ = 150.0, 139.0, 128.7, 128.4, 127.7, 117.5, 116.4, 110.7, 101.5, 81.3, 76.0, 51.5, 50.7, 29.7, 26.9, 26.8, 26.6, 20.3. Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.80; N, 13.49. Found: C, 69.54; H, 6.82; N, 13.41.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-4,7-bis[(ethoxycarbonyl)-methyl]-5,6-*O*-isopropylidene-1,3-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (6a). A 15.0 g (29.26 mmol) amount of **3a** gave 10.6 g (68%) of **6a**. $[\alpha]^{20}_D$ +43.7° ($CHCl_3$, c = 1.26); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.42−7.25 (m, 10 H); 5.08 and 4.08 (AB, J = 13.1 Hz, 4 H); 4.12 (q, J = 7.1 Hz, 4 H); 4.10 (m, 2 H); 3.48 (m, 2 H); 2.57 (ABX, 4 H); 1.28 (t, J = 7.1 Hz, 6 H); 1.19 (s, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 171.0, 161.8, 138.0, 129.1, 128.6, 127.6, 110.4, 74.7, 60.9, 55.2, 53.8, 32.1, 26.4, 14.1. Anal. Calcd for $C_{30}H_{38}N_2O_7$: C, 66.90; H, 7.11; N, 5.20. Found: C, 66.54; H, 7.02; N, 5.26.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-1,3-bis(cyclopropylmethyl)-4,7-bis[(ethoxycarbonyl)methyl]-5,6-*O*-isopropylidene-2*H*-1,3-diazepin-2-one (6b). A 1.75 g (4.13 mmol) amount of **3b** gave 1.07 g (62%) of **6b**. $[\alpha]^{20}_D$ +33.9° ($CHCl_3$, c = 0.76); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 4.27 (dddd, J = 7.4, 6.8, 2.0 and 1.6 Hz, 2 H); 4.12 (q, J = 7.1 Hz, 4 H); 4.01 (m, 2 H); 3.61 and 2.94 (ABX, 4 H, J_{AB} = 14.1 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.8 Hz); 2.79 and 2.69 (ABX, J_{AB} = 15.8 Hz, J_{AX} = 8.3 Hz, J_{BX} = 5.5 Hz, 4 H); 1.40 (s, 6 H); 1.24 (t, J = 7.1 Hz, 6 H); 1.05 (m, 2 H); 0.54 (m, 4 H); 0.26 (m, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 171.1, 161.2, 110.7, 75.4, 60.8, 56.3, 54.8, 32.3, 26.6, 14.1, 10.6, 4.6, 3.3. Anal. Calcd for $C_{24}H_{38}N_2O_7$: C, 61.78; H, 8.21; N, 6.00. Found: C, 61.63; H, 8.25; N, 6.03.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-4,7-bis(cyanomethyl)-5,6-*O*-isopropylidene-1,3-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (6c). A 444 mg (1.06 mmol) amount of **3c** gave 300 mg (64%) of **6c**. Mp 142−144 °C; $[\alpha]^{20}_D$ −32.4° ($CHCl_3$, c = 0.51); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.45−7.27 (m, 10 H); 5.02 and 4.37 (AB, 4 H, J = 14.4 Hz); 3.94 (dddd, J = 8.6, 5.4, 2.2 and 1.4 Hz, 2 H); 3.48 (dd, J = 2.2 and 1.4 Hz, 2 H); 2.59 and 2.47 (ABX, J_{AB} = 16.9 Hz, J_{AX} = 5.4 Hz, J_{BX} = 8.6 Hz, 4 H); 1.29 (s, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 159.7, 137.3, 129.2, 129.0, 128.5, 116.8, 111.5, 73.9, 56.0, 53.4, 26.4, 15.3. Anal. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 70.03; H, 6.41; N, 12.58.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-4,7-bis(cyanomethyl)-1,3-bis-(cyclopropylmethyl)-5,6-*O*-isopropylidene-2*H*-1,3-diazepin-2-one (6d). A 370 mg (1.06 mmol) amount of **3d** gave 242 mg (63%) of **6d**. $[\alpha]^{20}_D$ −30.5° ($CHCl_3$, c = 0.88); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 4.11 (dddd, J = 8.4, 5.8, 2.3 and 1.3 Hz, 2 H); 3.92 (dd, J = 2.3 and 1.3 Hz, 2 H); 3.62 and 3.11 (ABX, J_{AB} = 14.2 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.7 Hz, 4 H); 2.83 and 2.75 (ABX, J_{AB} = 16.8 Hz, J_{AX} = 8.4 Hz, J_{BX} = 5.8 Hz, 4 H); 1.46 (s, 6 H); 1.04 (m, 2 H); 0.60 (m, 4 H); 0.28 (m, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 159.6, 150.7, 116.8, 111.8, 74.4, 56.9, 54.5, 26.6, 15.4, 10.4, 4.1, 3.5. Anal. Calcd for $C_{20}H_{28}N_4O_3$: C, 64.49; H, 7.58; N, 15.04. Found: C, 64.25; H, 7.53; N, 14.98.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-5,6-dihydroxy-4,7-bis[(ethoxycarbonyl)methyl]-1,3-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (7a). A 49 mg (0.09 mmol) amount of **6a** gave 35 mg (78%) of **7a**. $[\alpha]^{20}_D$ +174.1° ($CHCl_3$, c = 0.58); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.41−7.22 (m, 10 H); 4.96 and 3.96 (AB, J = 14.1 Hz, 4 H); 4.12 (q, J = 7.1 Hz, 4 H); 3.87 (m, 2 H); 3.25 (bs, 2 H); 2.82 (bs, 2 H); 2.63 (ABX, 4 H); 1.27 (t, J = 7.1 Hz, 6 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 172.4, 162.0, 137.9, 129.5, 128.7, 127.7, 70.8, 61.1, 56.9, 54.4, 32.0, 14.1. Anal. Calcd for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 64.89; H, 6.94; N, 5.58.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-1,3-bis(cyclopropylmethyl)-5,6-dihydroxy-4,7-bis[(ethoxycarbonyl)methyl]-2*H*-1,3-diazepin-2-one (7b). A 50 mg (0.11 mmol) amount of **6b** gave 37 mg (68%) of **7b**. $[\alpha]^{20}_D$ −31.8° ($CHCl_3$, c = 0.73); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 4.27 (dddd, J = 7.4, 6.8, 2.0 and 1.6 Hz, 2 H); 4.12 (q, J = 7.1 Hz, 4 H); 4.01 (m, 2 H); 3.61 and 2.94 (ABX, 4 H, J_{AB} = 14.1 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.8 Hz); 2.79 and 2.69 (ABX, J_{AB} = 15.8 Hz, J_{AX} = 8.3 Hz, J_{BX} = 5.5 Hz, 4 H); 1.40 (s, 6 H,); 1.24 (t, J = 7.1 Hz, 6 H); 1.05 (m, 2 H); 0.54 (m, 4 H); 0.26 (m, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 172.5, 161.5, 71.3, 61.0, 58.6, 55.8, 32.1, 14.1, 10.5, 4.1, 3.4. Anal. Calcd for $C_{21}H_{34}N_2O_7$: C, 59.14; H, 8.04; N, 6.57. Found: C, 59.21; H, 8.07; N, 6.52.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-4,7-bis(cyanomethyl)-5,6-dihydroxy-1,3-bis(phenylmethyl)-2*H*-1,3-diazepin-2-one (7c). A 20 mg (0.05 mmol) amount of **6c** gave 15 mg (82%) of **7c**. $[\alpha]^{20}_D$ −13.8° ($CHCl_3$, c = 0.82); ^{1}H-NMR (250 MHz; $CDCl_3$): δ = 7.41−7.27 (m, 10 H); 5.09 and 4.13 (AB, J = 14.3 Hz, 4 H); 3.73 (bd, J = 7.8 Hz, 2 H); 3.25 (bs, 2 H); 3.21 (bs, 2 H); 2.72 and 2.57 (ABX, J_{AB} = 17.0 Hz, J_{AX} = 4.3 Hz, J_{BX} = 7.8 Hz, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$): δ = 160.3, 136.7, 129.2, 129.1, 128.4, 117.7, 69.7, 57.5, 55.4, 14.7. Anal. Calcd for $C_{23}H_{24}N_4O_3$: C, 68.30; H, 5.98; N, 13.85. Found: C, 68.02; H, 5.86; N, 13.72.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-4,7-bis(cyanomethyl)-1,3-bis-(cyclopropylmethyl)-5,6-dihydroxy-2*H*-1,3-diazepin-2-one (7d). A 31 mg (0.08 mmol) amount of **6d** gave 16 mg (60%) of **7d**. Mp 217−222 °C; ^{1}H-NMR (250 MHz; $CDCl_3$/CD_3OD; 60 °C): δ = 3.87 (m, 2 H); 3.75 (m, 2 H); 3.71 and 2.98 (ABX, J_{AB} = 14.2 Hz, J_{AX} = 7.4 Hz, J_{BX} = 6.8 Hz, 4 H); 2.95 (ABX, 4 H); 1.03 (m, 2 H); 0.61 (m, 4 H); 0.29 (m, 4 H). ^{13}C-NMR (62.9 MHz; $CDCl_3$/CD_3OD; 60 °C): δ = 161.2, 119.2, 70.7, 60.0, 57.4, 15.6, 11.4, 4.8, 4.3. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C, 61.43; H, 7.28; N, 16.85. Found: C, 61.24; H, 7.32; N, 16.76.

Diethyl (2*R*,3*S*,4*S*,5*R*)-5-[(cyclopropylmethyl)amino]-3,4-*O*-isopropylidene-2-[(phenylmethyl)amino]-1,6-hexanedicarboxylate (8): $[\alpha]^{20}_D$ −29.9° ($CHCl_3$, c = 0.94); ^{1}H-NMR (500 MHz; $CDCl_3$): δ = 7.34−7.02 (m, 5 H); 4.14 (m, 6 H); 3.92 and 3.77 (AB, J = 13.1 Hz, 2 H); 2.60 (ABX, J_{AB} = 15.1 Hz, J_{AX} = 6.3 Hz, J_{BX} = 6.5 Hz, 2 H); 3.21 (dt, J = 6.4 and 3.3 Hz, 1 H); 3.16 (ddd, J = 6.9, 6.0 and 3.6 Hz, 1 H); 2.53−2.42 (m, 4 H); 1.39 (s, 3 H); 1.66 (bs, 2 H); 1.36 (s, 3 H); 1.26 (t, J = 7.1 Hz, 3 H); 1.25 (t, J = 7.1 Hz, 3 H); 0.88 (m, 1 H); 0.43 (ABXY, 2 H); 0.08 (ABXY, 2 H); ^{13}C-NMR (125.8 MHz; $CDCl_3$): δ = 172.3, 172.2, 140.5, 128.3, 128.1, 126.9, 108.6, 79.1, 78.8, 60.5, 60.4, 54.9, 54.6, 52.5, 51.5, 36.8, 36.7, 27.2, 14.2, 11.4, 3.3, 3.1. Anal. Calcd for $C_{26}H_{40}N_2O_6$: C, 65.52; H, 8.46; N, 5.88. Found: C, 65.61; H, 8.43; N, 5.89.

(4*R*,5*S*,6*S*,7*R*)-Hexahydro-3-(cyclopropylmethyl)-4,7-bis[(ethoxycarbonyl)methyl]-5,6-*O*-isopropylidene-1-(phenylmethyl)-2*H*-1,3-diazepin-2-one (9): $[\alpha]^{20}_{D}$ −11.3° ($CHCl_3$, $c = 1.14$); ^{1}H-NMR (500 MHz; $CDCl_3$): $\delta = 7.40-7.28$ (m, 5 H); 4.97 and 4.04 (AB, $J = 14.2$ Hz, 2 H); 4.27 (ddd, $J =$ 9.0, 5.0, and 4.3 Hz, 1 H); 4.13 (m, 5 H); 3.96 (dd, $J = 9.7$ and 4.3 Hz, 1 H); 3.72 and 2.98 (ABX, $J_{AB} = 14.2$ Hz, $J_{AX} = 7.4$ Hz, $J_{BX} = 6.8$ Hz, 2 H); 3.58 (dd, $J = 9.7$ and 4.3 Hz, 1 H); 2.70 and 2.61 (ABX, $J_{AB} = 15.8$ Hz, $J_{AX} = 9.0$ Hz, $J_{BX} = 5.0$ Hz, 2 H); 2.67 (ABX, 2 H); 1.34 (s, 3 H); 1.27 (m, 9 H); 1.08 (m, 1 H); 0.56 (ABXY, 2 H); 0.29 (ABXY, 2 H); ^{13}C-NMR (125.8 MHz; $CDCl_3$): $\delta =$ 171.1, 171.0, 161.4, 138.2, 129.2, 128.7, 127.6, 110.6, 75.2, 75.0, 60.9, 56.7, 55.0, 53.8, 32.6, 31.9, 26.6, 26.5, 14.1, 10.7, 4.1, 3.3. Anal. Calcd for $C_{27}H_{38}N_2O_7$: C, 64.52; H, 7.62; N, 5.57. Found: C, 64.34; H, 7.58; N, 5.52.

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