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General Synthesis of Unsymmetrical Norbornane Scaffolds as Inducers for Hydrogen Bond Interactions in Peptides†,‡

Christian P. R. Hackenberger, Ingo Schiffers, Jan Runsink, and Carsten Bolm*

Institut für Organische Chemie der RWTH Aachen, Prof.-Pirlet-Str. 1, D-52056 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

Received September 23, 2003

Starting from readily accessible *endo-cis*-(2*S*,3*R*)-norbornene dicarboxylic acid benzyl monoester, a general and efficient synthetic approach toward unsymmetrical two-stranded peptidic structures was developed. In these structures the peptide strands are oriented in a parallel geometry. Their synthesis is easily applicable to a variety of amino acids and peptides. Specifically, a norbornane template as molecular scaffold induces hydrogen bonding between the adjacent peptide strands. The specific hydrogen bonding patterns between these strands were revealed by detailed NMR analysis including TOCSY/NOE experiments.

Introduction

The synthesis of compounds with defined secondary structures has recently become an emerging field in modern organic chemistry.[1] Along these lines, the desire for efficient procedures to assemble stable secondary structures has increased considerably.[2] Particular attention has been focused on the synthesis and structural investigation of β-sheets and β-hairpins.[3] The latter are considered to represent the smallest possible sheet structure and have been studied extensively as β-sheet model systems.[4] Several examples of such model systems as well as sheet mimetics are known to date,[5] which can be aligned in a parallel[6] or antiparallel fashion.[7] A common approach uses a molecular scaffold,[8] which preorients adjacent peptide strands and initiates noncovalent interactions and hydrogen bonds between them.[9] Besides covalent molecular scaffolds, a noncovalent linked framework has been reported recently.[10] Many of these systems are easily accessible and display stable sheetlike structures. However, they sometimes bear disadvantages in terms of general applicability since their syntheses allow only derivatives with equal peptidic side chains, which are attached to the molecular scaffold.

Our studies have focused on parallel peptide scaffolds containing a norbornene or norbornane motif. Norbornene scaffolds, which have been studied by Ranganathan et al.[11] and by North and co-workers,[12] are considered to orient two peptide strands attached to the *endo-cis*-(2*S*,3*R*)-norbornene-dicarbonyl substituents in the same direction, thus leading to hydrogen bonding patterns between the strands. However, the synthetic routes to these useful norbornene derivatives have severe limitations, as either unsymmetrical scaffolds are inaccessible or proline is required in one of the peptide strands. Therefore we initiated a study on searching for a novel strategy that allows the incorporation of almost any amino acid or peptide into the *endo*-norbornene framework.

* To whom correspondence should be adressed. Phone: +49 241 809 4675. Fax: +49 241 809 2391.

† This work is part of the Ph.D. thesis of C.P.R.H.

‡ Dedicated to Professor Dr. H.-J. Reich on the occasion of his 60th birthday.

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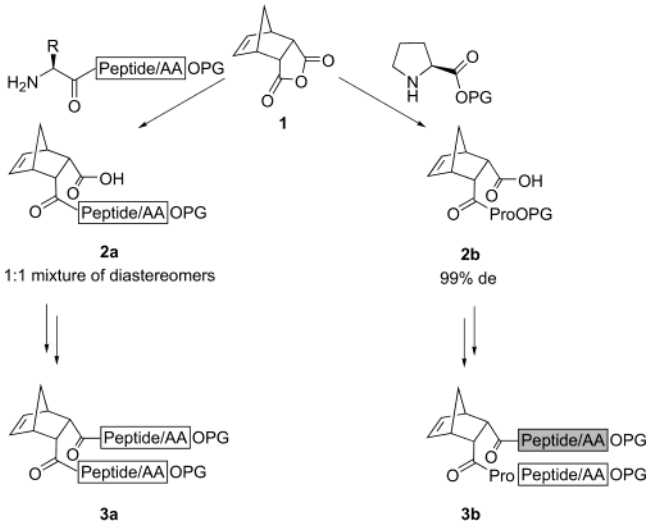
10.1021/jo030295+ CCC: $27.50
Published on Web 12/25/2003

SCHEME 1. Known Synthetic Approaches toward Peptides Containing a Norbornene Molecule



The known synthetic approaches toward *endo*-norbornene-containing peptides start out from norbornene anhydride **1** (Scheme 1). Ranganathan et al. produced a parallel C_2-symmetric peptide framework with two equivalent peptide strands (Scheme 1, left) by ring opening of **1** with primary amino acids or peptides to yield acid **2a** as a 1:1 mixture of diastereomers. To avoid difficult separations, the acid **2a** was symmetrized via coupling with the same amino acid or peptide to give the C_2-symmetric peptide **3a**. It was shown by CD measurements as well as X-ray studies that these norbornene templates initiate a β-sheet-like orientation.[13]

The approach by North led to the first example of an unsymmetrical norbornene template (Scheme 1, right). The key step in his procedure is a desymmetrization reaction of the norbornene anhydride **1**.[14] In contrast to the previous example the ring opening was performed with an ester of the seondary amino acid L-proline,[15] which gave acid **2b** in high yields and excellent diastereoselectivities.[16] Subsequent coupling steps led to strucutural defined pseudopeptides **3b** with up to six amino acids attached.[12,17] The main disadvantage in this route, however, is the requirement of proline at the first position of one peptide strand. Unfortunately, proline cannot be cleaved and exchanged to other amino acids under conditions that are desirable for peptidic systems. This lack of variation is even more important in the context of the peptides secondary structures as proline in combination with other amino acids is known to favor turn

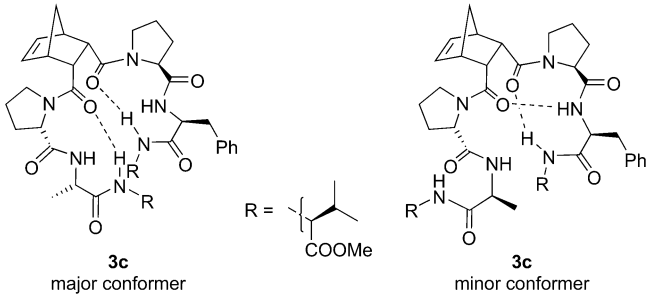


FIGURE 1. Hydrogen bonding patterns in unsymmetrical norbornene peptides.[12,17]

conformations,[18] which mainly results in *intra*strand interactions as depicted in Figure 1, where the two major conformers of a norbornene heptapeptide **3c** are illustrated.[19] This picture points to another goal of our studies, since we intended to search for other noncovalent interactions and especially *inter*strand hydrogen bonding patterns that can be initiated by such bicyclic scaffolds. We assumed those to be dependent on the kind of amino acids in the norbornene or norbornane peptide backbone.

Results and Discussion

As outlined in the Introduction, our first aim was to generalize the synthetic approach to unsymmetrical norbornene peptides aligned in a parallel orientation. We started our investigation by applying another desymmetrization procedure, which circumvents the synthetic disadvantages mentioned above, i.e., the alkaloid-mediated desymmetrization of anydrides with alcohols.[20] When performed with methanol this protocol leads to enantiomerically pure norbornene hemimethylester **4** in high yields (Scheme 2). We envisioned **4** as the starting point in our synthesis of unsymmetrical parallel β-sheets.

First, norbornene hemiester **4** was coupled with various C-terminal protected amino acids, yielding in all cases norbornene amino acids **5a**−**e** in very good yields (Scheme 2 and Table 1).[21] Especially noteworthy is the fact that a possible alternative product, imide **6**, was not detected even in the conformationally flexible glycine analogue **5e**. Imide formation was the major side reaction in related systems with an anthracene backbone[22] and the one described by Ranganathan et al.[11] Next, the selective cleavage of one of the two ester functionalities in **5** was envisaged. Unfortunately, under various conditions this transformation remained unsuccessful. Base-mediated cleavage of **5b** led almost exclusively to imide **6a** with a free acid functionality (R^3 = H). The attempt to transform **5b** directly to the corresponding amide using a NaCN-catalyzed transamidation, as previously used for

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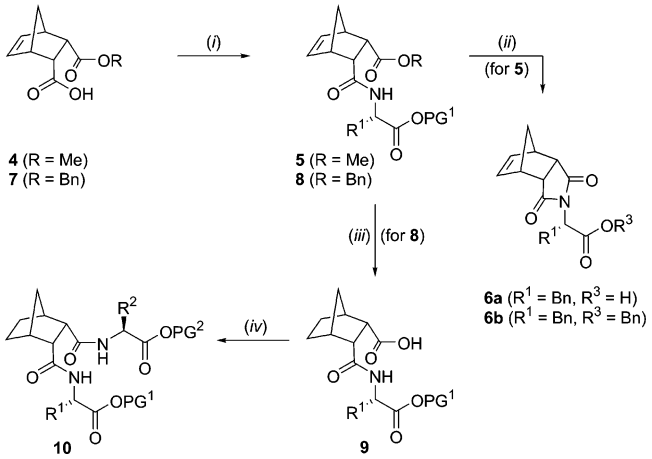
SCHEME 2. Synthesis of Unsymmetrical Parallel Norbornane Containing Peptides[a]



[a] Conditions: (i) HXaa[1]OPG[1] (see Table 1), DCC, DMAP, CH_2Cl_2; (ii) 1 N NaOH, MeOH (product **6a**) or NaCN, HYaa[2]OPG[2], MeOH (product **6b**); (iii) H_2, Pd/C; (iv) HYaa[2]OPG[2] (see Table 3), DCC, HOBt, DMAP, CH_2Cl_2.

TABLE 1. Carbodiimide Coupling of Norbornene Hemiesters with Amino Acids[a]

entry	hemiester	amino acid	product	yield [%]
1	**4**	HPheOBn	**5a**	74
2	*ent*-**4**	HPheOBn	**5b**	71
3	**4**	HPheO*t*Bu	**5c**	96
4	**4**	HLeuOBn	**5d**	99
5	**4**	HGlyO*t*Bu	**5e**	93
6	**7**	HGlyO*t*Bu	**8a**	70
7[b]	**7**	HGlyO*t*Bu	**8a**	98
8	**7**	HAlaOMe	**8b**	76
9[b]	**7**	HAlaOMe	**8b**	94
10	**7**	HPheO*t*Bu	**8c**	85

[a] The reactions were performed at room temperature for 12 h using 1 equiv of C-terminal protected amino acid, 1 equiv of HOBt, 0.1 equiv of DMAP, and 1.1 equiv of DCC in CH_2Cl_2. [b] As coupling reagent EDC was used instead of DCC.

the synthesis of *endo*/*exo* amino alcohol amides,[23] resulted in imide formation as well. This time, however, the benzyl ester (R^3 = Bn) remained intact and imide **6b** was formed.

Because the approach toward the unsymmetrical bicyclic scaffolds using desymmetrized norbornene hemimethylesters **4** was not successful, we revised our strategy and chose the norbornene hemibenzylester **7** as starting material. As recently described by our laboratory this hemiester can be prepared in 92% yield and 97% ee by an analogous anhydride opening in the presence of an alkaloid using benzyl alcohol as nucleophile.[24] This change in the ester functionality allows a mild ester cleavage by simple hydrogenation. The amino acids should then be protected as inert C-terminal esters in the first coupling step, and commercially available methyl and *tert*-butyl esters would be starting materials of choice. During the hydrogenation of the benzyl esters we expected the norbornene double bond to be reduced affording the analogous norbornane derivatives. However, because both bicyclic scaffolds have similar rigidities, only a minor influence on the sheet inducing propensities should result.[23]

TABLE 2. Deprotection of Benzyl Esters under Hydrogenation Conditions[a]

entry	benzyl ester	R^1	PG^1	product	yield [%]
1	**8a**	H	*t*Bu	**9a**	85
2	**8b**	Me	Me	**9b**	97
3	**8c**	Bn	*t*Bu	**9c**	99

[a] The reactions were performed with H_2 (1 atm) at room temperature in ethyl acetate (0.25 M solution). The conversions were monitored by TLC.

The coupling of norbornene benzylester **7** with various amino acids to norbornene amino acids **8a**−**c** proceeded with similar high yields as in the methyl ester cases (Scheme 2 and Table 1, entries 6−10). Entries 7 and 9 are particularly noteworthy because in these reactions EDC (instead of DCC) was the coupling reagent and the workup by aqueous acidic extraction led to almost quantitative product yields without further purification by column chromatography.

Consequently, compounds **8a**−**c** were hydrogenated with Pd/C as catalyst, giving rise to the corresponding norbornane acids **9a**−**c** in very good yields (Scheme 2 and Table 2). Attempts to retain the norbornene double bond by shorter reaction times failed.

Acids **9b** and **9c** were then coupled under DCC/HOBt conditions to give bis(amino acid diesters) **10** in good yields, which demonstrated the general approach toward unsymmetrical norbornane peptides **10**. Starting form norbornene anydride **1** this synthetic route yields peptide derivatives with overall yields >72% over four steps (Scheme 2 and Table 3). Additionally, the mild cleavage conditions of the benzyl ester allows an applicability of this reaction sequence to almost any amino acid with no racemization or side reaction in the peptide chain.

Having established the general synthetic strategy, we adressed the questions of how these bis(amino acid diesters) behave in terms of structural orientation and if they show any significant difference from the known norbornene proline derivatives. Investigations of the ^{1}H NMR amide proton shifts of derivatives **10a**−**c** revealed signals between 6.26 and 6.90 ppm (see Supporting Information), which have also been observed in the related systems by North.[12] Generally, these amide hydrogens, which are close to the bicyclic scaffold, do not seem to be involved in hydrogen bonding to a major extend. We therefore decided to search for interstrand molecular interactions in longer peptides and prepared norbornane peptide **13**. The synthesis proceeded analogously to the one of norbornane peptides **10** and involved a carbodiimide coupling of norbornene hemiester **7** with HPheAlaOMe to **11**, subsequent hydrogenation, and final coupling of the resulting acid **12** with HPheGlyOBn to **13** in good overall yields (Scheme 3).

^{1}H NMR analysis of compound **13** in $CDCl_3$ showed four amide proton signals at 5.97, 6.66, 7.74, and 7.82

(23) A disadvantage of the resulting saturated bicyclic scaffold is that it does not allow a direct access to interesting ROMP-peptide polymers or further chemical transformations as shown in related studies. For examples see ref 16 and (a) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518. (b) Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 2033. (c) Bolm, C.; Dinter, C. L.; Schiffers, I.; Defrère, L. *Synlett* **2001**, 1875 and references therein.

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TABLE 3. Coupling of Norbornane Acids to Unsymmetrical Parallel Bis(amino acid diesters) 10[a]

entry	norbornane acid	R^1	PG^1	amino acid	product	R^2	PG^2	yield [%][b]
1	**9b**	Me	Me	HPheO*t*Bu	**10a**	Bn	*t*Bu	79 (72)
2	**9c**	Bn	*t*Bu	HLeuOBn	**10b**	*i*Bu	Bn	85 (72)
3	**9c**	Bn	*t*Bu	HPheOMe	**10c**	Bn	Me	91 (77)

[a] The reactions were performed at room temperature for 12 h using 1 equiv of C-terminal protected amino acid, 1 equiv of HOBt, 0.1 equiv of DMAP, and 1.1 equiv of DCC in CH_2Cl_2. [b] Values in parentheses refer to overall yields after four steps starting from anhydride **1**.

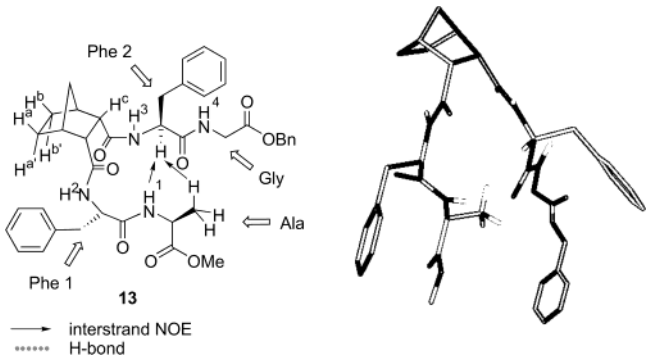
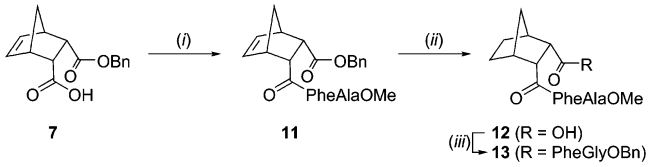


FIGURE 2. Interstrand NOEs in norbornane peptide **13** and structure of **13** after molecular dynamics using the AMBER force field.

SCHEME 3. Synthesis of Peptide 13[a]



[a] Conditions: (i) HPheAlaOMe, DCC, HOBt, DMAP, CH_2Cl_2 (71%); (ii) H_2, Pd/C (96%); (iii) HPheGlyOBn, DCC, HOBt, DMAP, CH_2Cl_2 (71%).

TABLE 4. ^{1}H NMR Amide Proton Signals in Norbornene Peptide 13[a]

entry	shift value [ppm]	signal (coupling constant)	Δ shift [ppm][b]	correlation
1	5.97	doublet (J = 8.0 Hz)	1.07	NH^2
2	6.66	doublet (J = 8.8 Hz)	1.50	NH^3
3	7.74	triplet (J = 5.5 Hz)	0.27	NH^4
4	7.82	doublet (J = 7.4 Hz)	0.35	NH^1

[a] The ^{1}H NMR data were recorded at 500 MHz in $CDCl_3$ and are given relative to TMS as internal standard. [b] DMSO (12 vol %) was added; $\Delta\delta$ $CHCl_3$ = 0.37 ppm.

ppm. A triplet at 7.74 ppm corresponded to the α-position to the methylene glycine moiety. Further correlations were made by NOE, TOCSY, and gHSQC spectra analyses (Table 4 and Figure 2).

As revealed by the data listed in Table 4, the signals of the remote amide protons NH^1 and NH^4 were significantly shifted downfield with respect to protons NH^2 and NH^3 in the proximity to the norbornane scaffold, indicating the presence of an interstrand hydrogen bond pattern involving the first two amide protons. Evidence for such interaction was also obtained from a DMSO titration experiment. Whereas NH^2 and NH^3 shifted significantly upon addition of 12 vol % of DMSO ($\Delta\delta$ = 1.07 and 1.50 ppm, respectively), the shift values for NH^1 and NH^4 were effected to a much lower extend ($\Delta\delta$ = 0.35 and 0.27 ppm, respectively). To determine the exact nature of the interstrand interactions, a number of selective DPFGSE-NOE and -TOCSY and a pseudo 3D TOCSY-NOE sequence were used.[26] Strong NOEs between NH^2 and $H^{a'}$ and NH^3 and H^c revealed the connection of the amides and the norbornane units. Furthermore, the transoid orientation of the two connecting amide carbonyl groups was indicated. Two more NOEs were found between the two peptide strands. Both involved the CH at the stereogenic center of phenylalanine. One NOE was detected between this group and the alanine methyl and the other between the CH and amide proton NH^1 (Figure 2, left). This observation confirmed the formation of a hydrogen bond between NH^1 and the carbonyl of the second amino acid, which was already indicated by the downfiled shift of amide proton NH^1. Taking the interstrand NOEs as molecular constraints, a molecular dynamics simulation of the norbornene peptide **13** with the program INSIGHT II using the force field AMBER[27] was carried out.[28] The resulting structure, which has a preferred conformation with an *inter*strand H-bond involving the amide proton NH^1, is shown in Figure 2. In comparison with norbornene peptide **3c** by North[12,17] bearing two proline residues in the peptide chain the observed hydrogen pattern in **13** differs significantly. Whereas in molecule **3c** mainly interactions *within* the peptide strands are observed, **13** clearly displays an interstrand hydrogen bond.

In contrast to NH^1 no interstrand NOE was observed for amide NH.[4] Thus the origin of the downfield shift of NH^4 could not be explained thoroughly. The molecular dynamic studies indicated that this effect could be a result of a positive anisotropic effect due to the aromatic residues of the phenylalanine side chain.

Conclusion

A general and mild synthetic procedure for the preparation of unsymmetrical template molecules that inititate a hydrogen bonding pattern between two adjacent peptide strands was developed. It takes advantage of the readily accessible norbornene anydride **1** and its efficient alkaloid-mediated asymmetric anhydride opening with benzyl alcohol to give desymmetrized benzyl ester **7**. Currently we are investigating further applications of the

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norbornane templates in larger β-sheet mimetics in both parallel and antiparallel orientations.

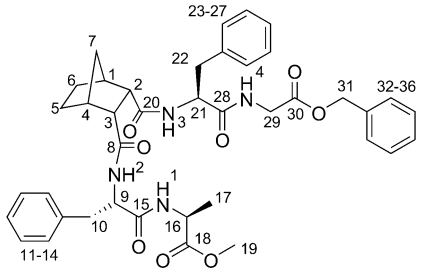
Experimental Section

General. Solvent purification, suppliers, instruments, and workup procedures, as well as the general procedures for the carbodiimide couplings (GP-A1 and GP-A2 for the DCC- and the EDC-coupling, respectively) and the deprotection of benzyl ester derivatives to acids under hydrogenation conditions (GP-B), are described in the Supporting Information.

(2*S*,3*R*)-3-*endo*-[1-(1-Methoxycarbonyl-ethylcarbamoyl)-2-phenyl-ethylcarbamoyl]-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid benzyl ester (11) was obtained from **7** by coupling with HPheAlaOMe according to GP-A1 as a colorless solid in 71% yield: mp 80 °C; $[\alpha]^{25}_D$ −34.1 (*c* 0.50, $CHCl_3$); R_f = 0.20 (PE/EE 1:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (1 H, d, J = 10.4 Hz), 1.34 (3 H, d, J = 7.1 Hz), 1.46 (1 H, td, J = 1.7, 10.4 Hz), 2.91 (1 H, dd, J = 7.2, 13.9 Hz), 3.01−3.04 (1 H, m), 3.10−3.18 (2 H, m), 3.20/3.32 (2 H, dAB-system, J = 3.2, 10.1 Hz), 3.69 (3 H, s), 4.45 (1 H, qn, J = 7.1 Hz), 4.56 (1 H, td, J = 6.0, 7.4 Hz), 4.92/5.08 (2 H, AB-system, J = 12.4 Hz), 5.93 (1 H, dd, J = 2.9, 5.7 Hz), 6.05 (1 H, d, J = 7.4 Hz), 6.34 (1 H, dd, J = 2.9, 5.7 Hz), 6.52 (1 H, d, J = 7.1 Hz), 7.18−7.30 (10 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 37.5, 46.1, 46.9, 48.3, 48.7, 49.3, 50.1, 52.4, 54.2, 66.4, 127.0, 128.1, 128.3, 128.5, 128.7, 129.4, 133.4, 136.0, 136.5, 136.7, 170.5, 171.6, 172.7, 172.8; IR ($CHCl_3$) ν 3294, 3065, 2978, 2935, 1745, 1646, 1544, 1453, 1382, 1340, 1211, 1165, 744, 699 cm^{-1}; MS (EI, DIP) *m*/*z* 505 (7, [M^+ + H]), 504 (22, [M^+]), 396 (41), 234 (13), 210 (14), 174 (24), 91 (100); HRMS calcd for $C_{29}H_{32}N_2O_6$ 504.226037, found 504.226070.

(2*S*,3*R*)-3-*endo*-[1-(1-Methoxycarbonyl-ethylcarbamoyl)-2-phenyl-ethylcarbamoyl]-bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (12) was obtained from **11** according to GP-B as a colorless solid in 96% yield: mp 93 °C; $[\alpha]^{25}_D$ −26.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (3 H, d, J = 7.1 Hz), 1.39−1.44 (2 H, m), 1.52−1.72 (2 H, m), 1.88−1.98 (2 H, m), 2.43−2.49 (1 H, m), 2.53−2.56 (1 H, m), 2.88 (1 H, dd, J = 3.0, 11.9 Hz), 2.93 (1 H, dd, J = 3.7, 11.9 Hz), 3.08 (2 H, dAB-system, J = 6.4, 13.9 Hz), 3.68 (3 H, s), 4.44 (1 H, qn, J = 7.1 Hz), 4.74 (1 H, td, J = 6.4, 8.0 Hz), 6.74 (1 H, d, J = 8.0 Hz), 6.98 (1 H, d, J = 7.1 Hz), 7.18−7.28 (5 H, m), 8.05 (1 H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 23.7, 24.5, 37.8, 40.1, 40.3, 41.7, 47.5, 48.1, 48.3, 52.4, 54.3, 126.9, 128.5, 129.4, 136.5, 171.0, 172.9, 173.1, 176.0; IR ($CHCl_3$) ν 3307, 3065, 3031, 2955, 2878, 1741, 1648, 1543, 1453, 1293, 1212, 1157, 744, 700 cm^{-1}; MS (EI, DIP) *m*/*z* (%) 416 (1, [M^+]), 398 (12, [$M^+ - H_2O$]), 159 (16), 120 (100), 66 (24); HRMS calcd for $C_{22}H_{28}N_2O_6 - H_2O$ 398.183172, found 398.183125.

(2*S*,3*R*)-[2-({3-*endo*-[1-(Benzyloxycarbonyl-methylcarbamoyl)-2-phenyl-ethylcarbamoyl]-bicyclo[2.2.1]heptane-2-*endo*-carbonyl}-amino)-3-phenyl-propionylamino]-propionic acid methyl ester (13) was obtained from **12** according to GP-A1 as a colorless solid in 71% yield: mp 78 °C; $[\alpha]^{25}_D$ −23.5 (*c* 0.20, $CHCl_3$); R_f 0.45 (EE/PE/AcOH 90:9:1 v/v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05/1.20 (2 H, m, H−C6), 1.26/1.50 (2 H, m, H−C5), 1.33 (2 H, m, H−C7), 1.41 (3 H, d, J = 7.2 Hz, H−C17), 2.23 (2 H, m, H−C1, H−C4), 2.59 (1 H, d, J = 10.7 Hz, H−C3), 2.86 (1 H, dd, J = 4.6, 11.4 Hz, H−C2), 2.96/3.18 (2 H, dAB-system, J = 9.0, 14.0 Hz, H−C22), 3.08/3.32 (2 H, dAB-system, J = 5.5, 13.8 Hz, H−C10), 3.64 (3 H, s, H−C19), 3.97/4.13 (2 H, dAB-system, J = 5.5, 12.9 Hz, H−C29), 4.50 (1 H, qn, J = 7.2 Hz, H−C16), 4.58 (1 H, q, J = 6.0 Hz, H−C9), 4.75 (1 H, dt, J = 5.8, 8.8 Hz, H−C21), 5.10 (2 H, s, H−C31), 5.97 (1H, d, J = 8.0 Hz, NH-2), 6.66 (1 H, d, J = 8.8 Hz, NH-3), 7.16−7.36 (15 H, m, H−C11−14, H−C23−27, H−C32−36), 7.74 (1 H, t, J = 5.5 Hz, NH-4), 7.82 (1H, d, J = 7.4 Hz, NH-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3 (C-17), 23.1 (C-5), 25.3 (C-6), 36.3 (C-10), 37.3 (C-22), 38.7 (C-4), 40.7 (C-7), 41.5 (C-1), 41.6 (C-29), 47.4 (C-2), 48.5 (C-16), 49.9 (C-3), 52.4 (C-19), 53.6 (C-21), 53.7 (C-9), 67.0 (C-31), 126.7 (C-aryl), 126.9 (C-aryl), 128.2 (C-aryl), 128.4 (C-aryl), 128.4 (C-aryl), 128.6 (C-aryl), 128.7 (C-aryl), 129.2 (C-aryl), 129.3 (C-aryl), 135.4 (C-aryl), 137.0 (C-aryl), 137.1 (C-aryl), 169.9 (C═O), 170.9 (C═O), 171.8 (C═O), 172.3 (C═O), 172.7 (C═O), 173.7 (C═O); IR ($CHCl_3$) ν 3400, 3282, 3064, 2929, 2876, 2851, 1741, 1642, 1541, 1501, 1454, 1383, 1192, 753, 701 cm^{-1}; MS (EI, DIP) *m*/*z* 710 (1, [M^+]), 463 (1), 462 (7), 461 (25), 399 (24), 398 (16), 268 (44), 131 (37), 120 (100).



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Acknowledgment. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 "Asymmetric Synthesis by Chemical and Biological Methods". C.P.R.H. is grateful to the Fonds der Chemischen Industrie and the BMBF for a predoctoral stipend. We also thank Nicole Brendgen, Susi Grünebaum, and Marc Hans for experimental contributions, Dr. Marc Nitz for helpful discussions, Dr. Eugenio Vazques for help during the modeling studies, and Prof. Dr. Barbara Imperiali for the use of her modeling facilities.

Supporting Information Available: Full experimental details for all new compounds and spectral characterization (^{1}H NMR, ^{13}C NMR, gMQCOSY) of **5c**, **8c**, **9c**, **10a**, **10b**, **10c**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030295+