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3-Formylcyclopent-3-enyl- and 3-Carboxycyclopentylglycine Derivatives: A New Stereocontrolled Approach via Retro-aldol or Retro-Claisen Reactions

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A new synthetic approach to diastereomeric cyclopent-3-enylglycines **19/20**, functionalized on the ring with a formyl group, and to cyclopentylglycine, substituted with a carboxy group (compounds **21/22**), was devised by applying retro-aldol and retro-Claisen reactions, respectively, to diastereomeric 2-amino-3-ethoxycarbonyloxynorbornene-2-carboxylic acid derivatives **5**, **6** and to diastereomeric 2-amino-3-oxo-norbornane-2-carboxylic acid derivatives **17**, **18**. The goal of controlling the cis stereochemistry of the cyclopentyl substituents was reached using compounds **17**, **18**. A partial control of the stereochemistry of the amino acidic carbon was achieved starting from **17** and using sodium hydrogen carbonate in acetone/DMF. From *exo*-**17**, the acid **22** was obtained as the major diastereomer.

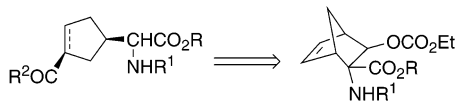
Introduction

Cyclopentylglycines are an interesting class of amino acids whose biological activity depends on the substituent on the cyclopentyl ring. Derivatives having an amidino group on C-3 inhibit the NO-synthase enzymes (NOS) responsible for the transformation of arginine into citrulline.[1] The inhibitory effect of a series of cyclopentylglycines functionalized on C-3 with an electron-withdrawing group toward the neuraminidase of the influenza virus is known.[2] Zang et al. reported the use of heterosubstituted cyclopentylglycines for the preparation of a new class of nucleoside analogues, i.e., the polioxines and nicoxines.[3] Finally, a compound in which the cyclopentyl ring of the above amino acid was condensed with a cyclohexyl ring was the key intermediate for the preparation of a sesquiterpene isolated from marine sponges of the *Axane* family.[4]

Few synthetic procedures are known for the preparation of cyclopentylglycine derivatives,[1−5] and all these start from functionalized cyclopentyl compounds that are then transformed into the above amino acids.

In continuing our research on the preparation of new amino acids[6−11] and on their use to obtain new derivatives, we now report an original synthesis of cyclopentylglycine derivatives functionalized on C-3 with a formyl or carboxy group. It is known that norbornane or norbornene derivatives with an appropriate electrophilic functionalization at C-2 and/or C-3 can be transformed into 1,3-disubstituted cyclopentene or cyclopentane derivatives by cleavage of the C2−C3 bond.[12] In our case, the key starting materials for the preparation of the above-mentioned compounds were the spiro compound **3** and the 2-aminonorbornene- or norbornane-2-carboxylic acid derivatives **5**, **6**−**17**, **18**, substituted on C-3 with an oxygen atom, some of which were recently prepared by our group. Taking advantage of retro-aldol or retro-Claisen reactions, in which the C2−C3 bond is involved, it was possible to obtain the cyclopentenyl- or cyclopentylglycine derivatives functionalized on the ring with a formyl or a carboxy group, respectively (Scheme 1). In the case of the saturated compounds, the stereochemistry

SCHEME 1



R^2 = H, OH

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(1) Eustache, J.; Grob, A.; Lam, C.; Sellier, O.; Schulz, G. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2961.

(2) Babu, Y. S.; Chand, P.; Montgomery, J. A. PTC Int. Appl. WO 47,194, 1997. *Chem. Abstr.* **1998**, *128*, 101850u.

(3) Zhang, D.; Miller, M. *J. Org. Chem.* **1998**, *63*, 755.

(4) Aggarwal, V. K.; Monteiro, N.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1997**, *62*, 4665.

(5) Guevel, A.-C.; Hart, D. J *J. Org. Chem.* **1996**, *61*, 473.

(6) Clerici, F.; Gelmi, M. L.; Pocar, D. *J. Org. Chem.* **1999**, *64*, 726.

(7) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**, *64*, 5764.

(8) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2000**, *65*, 6138.

(9) Clerici, F.; Gelmi, M. L.; Gambini, A., Nava D. *Tetrahedron* **2001**, *57*, 6429.

(10) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2001**, *66*, 4941.

(11) Abbiati, G.; Clerici, F.; Gelmi, M. L.; Gambini, A., Pilati, T. *J. Org. Chem.* **2001**, *66*, 6299.

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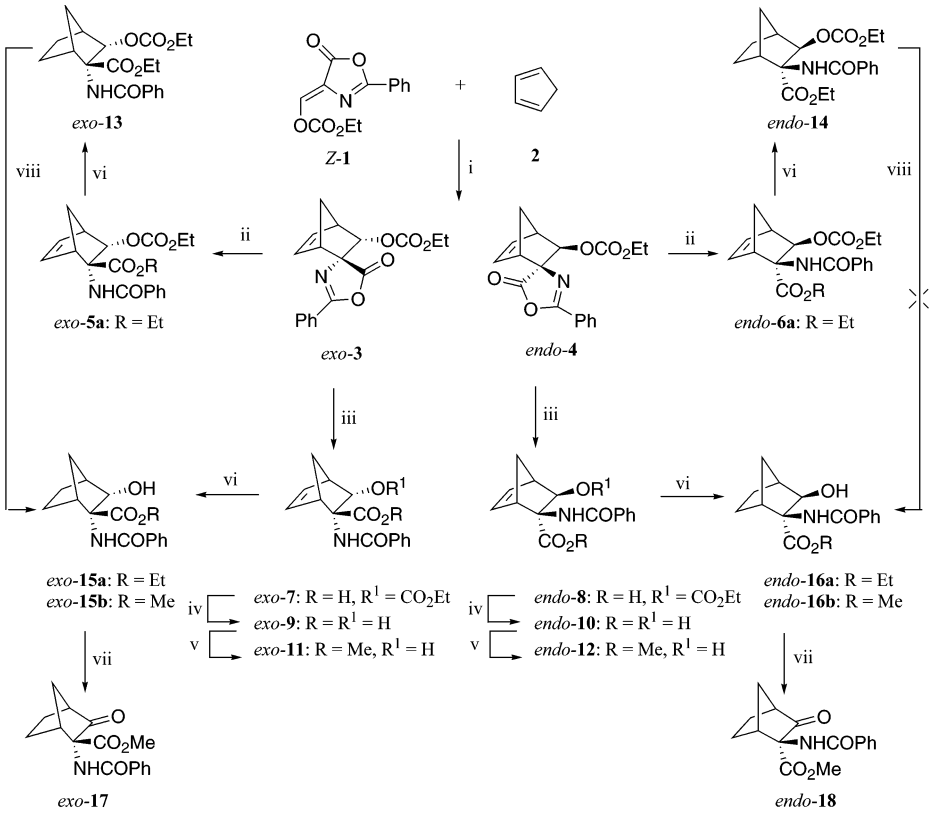
SCHEME 2[a]



[a] Reagents and conditions: (i) CH_2Cl_2, $Mg(ClO_4)_2$, 25 °C; (ii) EtOH, $(Bu_2ClSn)_2O$, reflux; (iii) THF, HCl; (iv) Me_2NH, EtOH, reflux; (v) CH_2Cl_2, CH_2N_2, −20 °C; (vi) H_2, Pd/C, EtOH; (vii) CH_2Cl_2, PCC; (viii) EtOH, Na_2CO_3.

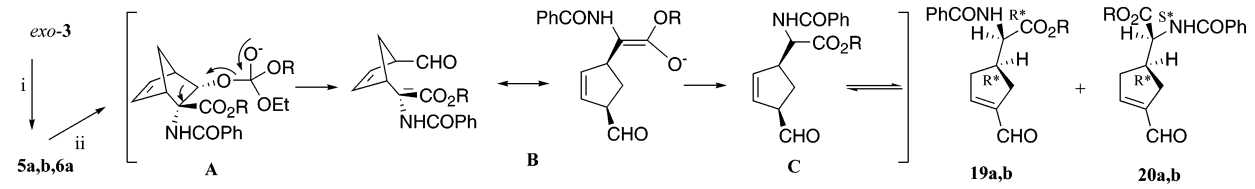
of both the substituents at C-1 and C-3 on the cyclopentyl ring was controlled independently by the configuration of the starting norbornane derivatives. By adopting this synthetic strategy, the cis relationship between the two substituents was assured. Stereochemical control on the α-carbon of the amino acidic moiety also was achieved.

Results

Diastereomeric ethyl 2-benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]hept-5-ene-2-yl-carboxylates *exo*-**3** and *endo*-**4** were the starting materials for the preparation of the cyclopentylglycines (Scheme 2). Compounds **3**, **4** are easily available by known reactions starting from cyclopentadiene **2** and ethyl 2-phenyl-5-oxo-oxazol-4-methylene-carbonate (*Z*)-**1** using a variety of Lewis acids as the catalysts to favor the Diels−Alder reaction.[8,11] Previous work on this reaction was supplemented by new studies on scale-up with the aim of increasing the yield and thus the availability of the starting materials. $Mg(ClO_4)_2$ was used as the catalyst for the cycloaddition reaction, and cycloadducts were obtained in good yield (87%, *exo*-**3**/*endo*-**4** ratio = 70:30) simply by washing the organic layer with water followed by crystallization of the products. Compounds *exo*-**3** and *endo*-**4** were sufficiently pure (^{1}H NMR) for further transformations. To increase the yield in the preparation of the esters *exo*-**5a** and *endo*-**6a**, a different procedure with respect to that reported[10] was found for the transformation of cycloadducts **3**, **4**. In fact, when cycloadducts *exo*-**3** and *endo*-**4** were treated with ethanol using bis-(dibutylchlorotin)oxide as the catalyst, the ethyl esters *exo*-**5a** and *endo*-**6a** were obtained in almost quantitative yields (85% overall yield from **1**). Acids *exo*-**7** and *endo*-**8** were obtained from *exo*-**3** and *endo*-**4**, respectively, according to a known procedure (87% overall yield from **1**).[8] Methyl esters *exo*-**11** and *endo*-**12** were obtained from *exo*-**7** and *exo*-**8**, respectively, after hydrolysis of the carbonate (intermediates *exo*-**9** and *endo*-**10**[8], respectively) and esterification with diazomethane. Starting from esters *exo*-**5** and *endo*-**6** and *exo*-**11** and *endo*-**12** and by reduction of the double bond, the norbornane derivatives *exo*-**13** and *endo*-**14** and *exo*-**15b** and *endo*-**16b**, respectively, were produced in quantitative yield. The direct oxidation of unsaturated hydroxy-ester *exo*-**11** with several oxidizing agents (e.g., pyridinium chlorochromate, PCC) resulted, in all cases, in a poor yield (10%) of the desired 3-oxo derivative. By contrast, starting from the saturated hydroxy ester *exo*-**15b** or from *endo*-**16b** and using PCC as the oxidant, the keto derivatives *exo*-**17** and *endo*-**18** were obtained in 95 and 40% yields, respectively. All new compounds were characterized spectroscopically and by elemental analysis, and the spectral data agreed well with the values known for similar compounds.[8,10,11] The presence of a keto group in compounds *exo*-**17** and *endo*-**18** was confirmed by a signal at δ 209.9 and 207.6, respectively, in the ^{13}C NMR spectrum.

(12) (a) Rainier, J. D.; Xu, Q. *Org. Lett.* **1999**, *1*, 27. (b) Kitano, K.; Katagiri, N.; Kaneko, C. *Chem. Lett.* **1994**, 1285. (c) Sato, M.; Takayama, K.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 2615 and references cited therein. (d) Chamberlain, P.; Rooney, A. E. *Tetrahedron Lett.* **1976**, *4*, 383.

SCHEME 3[a]



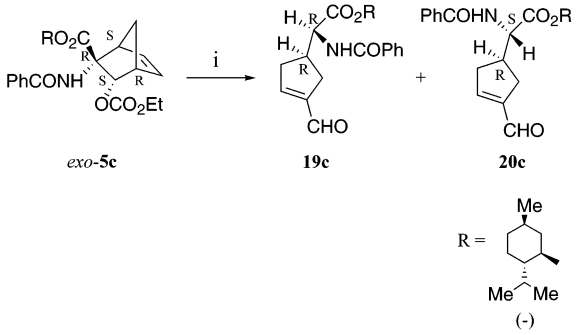
[a] Reagents and conditions: (i) MeOH, Na_2CO_3, reflux; (ii) EtOH, Na_2CO_3, reflux.

For the preparation of cyclopentylglycine derivatives functionalized with the formyl or carboxy groups at C-3, both the norbornene compounds **3**−**6** and **11** and the norbornane derivatives **13**, **14** and **17**, **18** were used either as the mixture of *exo*/*endo* compounds or, where convenient, as a single diastereomer. Different reaction conditions were studied to find the best way to perform the retro-aldol-like reaction. Only the unreacted starting material compounds or tarry compounds were obtained from the unsaturated 3-hydroxy-ester *exo*-**11** when operating with a variety of bases in different solvents (i.e., NaH/MeOH, F^-/18-crown-6/MeCN, N_3^-/18-crown-6/MeCN, Na_2CO_3/MeOH) and at different temperatures. Instead, treatment of esters *exo*-**5a** and *endo*-**6a** in ethanol and in the presence of sodium carbonate as the base at reflux afforded the protected diastereomeric 3-formylcyclopent-3-enylglycines **19a**, **20a** (Scheme 3). The same reaction was also carried out starting from either pure *exo*-**5a** or pure *endo*-**6a**. The *exo*-compound reacted faster (1 h; 82%) than the *endo* compound (2 h; 80%). Under similar conditions, the aldehydes **19b**, **20b** were obtained directly from the spiro oxazolone *exo*-**3**, via ester *exo*-**5b**. In fact, allowing *exo*-**3** to react with methanol in the presence of sodium carbonate rapidly (20 min) afforded compounds **19b** and **20b** in 70% yield. In all cases, a 1:1 mixture of the diastereomeric aldehydes was formed. It should be noted that the unsaturated aldehydes are unstable to strong bases (as well as to acids), which cause polymerization. This datum explains the behavior of hydroxy compound *exo*-**11**: weaker bases do not affect it, whereas stronger bases give tarry compounds.

The formation of aldehydes **19**, **20** (Scheme 3) can be explained as follows. Esters *exo*-**5** and *endo*-**6**, on reaction of the alkoxide ion with the carbonate group, afford intermediate **A**, which through the retro-aldol reaction gives the stabilized anion **B**. Protonation of the latter gives two diastereomeric β,γ-unsaturated aldehydes **C**, which isomerize to the thermodynamically more stable (3-formyl-3-cyclopentenyl)glycines **19**, **20**. Considering that the hydroxy ester *exo*-**11** did not react with sodium carbonate in EtOH, a previous transesterification step was excluded and **A** is confirmed as the true intermediate in this reaction. The diastereomeric aldehydes **19**, **20** were obtained in a 1:1 ratio independently from the reaction conditions. Thus, the electrophilic substitution must occur with the formation of enolate **B**, which is then protonated nonselectively.

Different base counterions and/or solvents were tested to verify the possibility of inducing diastereoselection at the C-α position of the amino acid moiety. Neither $MgCO_3$, Ag_2CO_3, $CdCO_3$, nor Li_2CO_3 in EtOH had any effect on compounds **5**, **6**. The same negative result was

SCHEME 4[a]



[a] Reagents and conditions: (i) EtOH, Na_2CO_3, reflux.

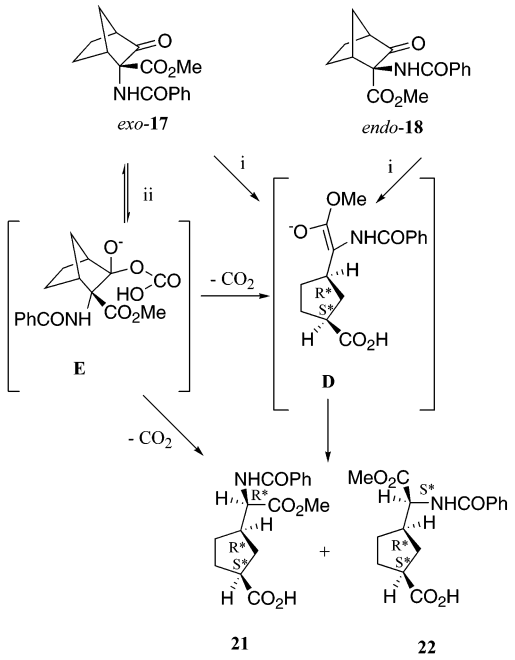
obtained using Na_2CO_3 in a hindered solvent such as *t*-butanol or in an apolar solvent like benzene with MeOH as the reactant or by using a strong base (LiOMe) in an apolar solvent (benzene). When a mixture of EtOH/DMF (10:1) and Na_2CO_3 were used, the reaction was slower (8 h) but the same 1:1 mixture of aldehydes (50%) was obtained. A different approach to controlling the stereochemistry at the amino acid carbon was tried in which the chiral (−)-menthyl ester *exo*-**5c**[11] was allowed to react under standard conditions (Scheme 4). However, in this case also the diastereomeric glycine derivatives **19c** and **20c** were obtained again in a 1:1 ratio. Thus, the chiral menthyl group is unable to influence the protonation of the intermediate carbanion **B**.

Although obtaining the new compounds **19**, **20** is an interesting synthetic result, the loss of chirality at C-3 caused by migration of the double bond is unfortunate. For this reason, the saturated ester *exo*-**13** was subjected to the retro-aldol reaction using Na_2CO_3 in ethanol. After 24 h at room temperature, only the hydroxy derivative *exo*-**15a** was formed, whereas when the reaction was carried out at reflux for 2 h, only *exo*-**15a** and tarry compounds were obtained (Scheme 2). On the other hand, *endo*-**14** was recovered unchanged when subjected to these conditions. Generally speaking, it appears that *exo* compounds are more reactive than their *endo* isomers, whereas the unsaturation in the ring favors the retro-aldol reaction probably because of ring strain.

To overcome the problem related to the poor reactivity of the saturated compounds, the β-ketoester derivatives *exo*-**17** and *endo*-**18** were prepared with the idea that a retro-Claisen reaction might afford better results than the retro-aldol reaction.

Starting from *exo*-**17** or a mixture of *exo*-**17** and *endo*-**18** and using pyridine both as the base and solvent led to no reaction, but adding water to the reaction mixture afforded two diastereomeric 3-(benzoylamino-methoxy-

SCHEME 5[a]



[a] Reagents and conditions: (i) pyridine/H_2O, reflux, then H_3O^+; (ii) $NaHCO_3$, acetone/DMF, reflux, then H_3O^+.

carbonylmethyl)cyclopentanecarboxylic acids **21** and **22** (Scheme 5) in good yield (83%) and in a 1:1 ratio. Compounds **21** and **22** are epimeric at C-α of the amino acid moiety, as demonstrated by ^{1}H NMR. Partial control of the stereochemistry at C-α could be realized by using $NaHCO_3$ in a mixture of acetone and DMF (9:1). In this case, ketone *exo*-**17** afforded compounds **21/22** in a 1:2 ratio, the major isomer having the *S** configuration at the α-position of the amino acid moiety, as demonstrated by spectroscopic analysis (see below). Considering these positive results, we examined **5** under the same reaction conditions. In this case, the reaction proceeded very slowly at room temperature, whereas when the reaction was heated, only tarry compounds were found.

The retro-Claisen reaction of *β*-ketoesters *exo*-**17** and *endo*-**18** in pyridine/water resulted in the racemization at the α-carbon in agreement with the formation of the enolate **D**, which is symmetrically protonated. This is not surprising because the other stereocenter is too far away from to the enolate ion to induce chirality. To explain the stereochemical outcome when $NaHCO_3$ in acetone/DMF was used and considering that the major isomer **22**, starting from *exo*-**17**, was formed with retention of configuration at the amino acid carbon following the cleavage of the C2−C3 bond, the hypothesis of Gassman et al.[13] is appropriate. In fact, on reaction of the bicarbonate ion with the carbonyl group, the intermediate **E** is formed, which can evolve to enolate **D** or proceed directly to the carboxy compound **22** via a six-membered intermediate that permits retention of the stereochemistry at C-α. It was found also that acid **21** does not isomerize under these reaction conditions, thus confirming this hypothesis.

(13) Gassman, P. G.; Lumb, J. T.; Zalar, F. V. *J. Am. Chem. Soc.* **1967**, *89*, 940.

The structure of cyclopentylglycine derivatives was confirmed by analytical and spectroscopic data, and in general, all signals were assigned by using COSY and HETCOR reverse experiments. The ^{1}H NMR spectrum of compound **19b** confirms the presence of the aldehydic proton (9.75 *δ*), the olefinic proton at 6.82 *δ*, and NH and amino acid protons at 6.69 *δ* (d, J = 8.5 Hz, exchangeable) and 5.00 *δ* (dd, J = 8.5, 5.7 Hz), respectively. Similar signals were found for isomer **20b** at 9.76, 6.82, 6.70 *δ* (d, J = 7.3 Hz) and 4.94 *δ* (dd, J = 8.0, 7.3 Hz). The position of the double bond was unequivocally assigned by a COSY experiment. The two isomeric chiral aldehydes **19c** and **20c** show similar spectra. The **19c** isomer shows signals for the CH amino acid proton at lower field (4.99 *δ*) and a larger J_{NH-CH} (8.5 Hz) value with respect to isomer **20c** (*CH*N: 4.93 *δ*, dd, J_{NHCH} = 6.8 Hz, J_{HCHCH} = 8.0 Hz). The structure for compound **20c** and its configuration are definitively confirmed by X-ray analysis from which the *S* and *R* configuration was assigned to the amino acid α-carbon and C-1 of cyclopentyl ring, respectively (Figure S1, Supporting Information).

From this result and on the basis of the ^{1}H NMR considerations reported above, we can assign indirectly the configuration to isomers **19a**,**b** and **20a**,**b** having the same *R** configuration at C-1 of the cyclopentyl ring and the *R** and *S** configuration, respectively, at the amino acid center.

Furthermore, because the C1−C2 bond is not broken, the stereochemical result reported above confirms indirectly the proposed[11] stereochemistry of ester *exo*-**5c**.

Acid compounds **21** and **22** show similar signals for the amino acid moiety. The first isomer presents signals at 7.12 *δ* (d, J = 8.0 Hz, NH) and 4.91 *δ* (dd, J = 8.0, 5.2 Hz, *CH*N), whereas the second shows signals at 6.89 *δ* (d, J = 7.3 Hz, NH) and 4.88 *δ* (dd, J = 7.3 Hz, 7.0 H, *CH*N). Considering the similarity between the spectra of the isomeric acids **21**, **22** and the aldehyde couple **19/20** both for the chemical shift of amino acid protons and the coupling constant values, we can assume the same *R** and *S** configuration at C-α for compounds **21** and **22**, respectively. Furthermore, because the C1−C2 and C3−C4 bonds of the norbornane ring were not involved in the retro-Claisen reaction, the 1*S** and 3*R** configuration was assigned both to **21** and **22**. In fact, the NOESY experiment of compound **22** revealed spatial proximity between H-3 (2.53 *δ*) and H-1 (2.88 *δ*) confirming the cis relationship between the two carbon atoms. Furthermore, the H-3 proton revealed a positive Overhauser effect with the cis protons H-4 (1.77 *δ*) and H-2 (2.15 *δ*) and between the latter proton and H-1.

In conclusion, new and original syntheses of 3-formylcyclopent-3-yl- and 3-carboxycyclopentylglycine derivatives were accomplished starting from the easily available 2-aminonorbornene- or norbornane-2-carboxylic acid derivatives substituted on C-3 with an oxygen substituent. The goal of controlling the stereochemistry on the cyclopentyl substituents was achieved by using the norbornane ring functionalized on C-3 with the more reactive *β*-keto group, which permitted the use of a weaker base for the retro-aldol and retro-Claisen reactions. Furthermore, partial control of the stereochemistry of the amino acid carbon was achieved by using sodium hydrogen carbonate in acetone/DMF, affording retention of configuration at the amino acid moiety in the major diastereo-

mer in agreement with an intramolecular protonation mechanism.

Experimental Section

Scale-up of the Cycloaddition Reaction. Oxazolone (*Z*)-**1a** (14.2 g, 0.054 mol) was dissolved in anhydrous CH_2Cl_2 (240 mL) under a nitrogen atmosphere and with stirring at room temperature. Diene **2** (7 g, 0.106 mol) and $Mg(ClO_4)_2$ (1.2 g, 0.0054 mol) were added. After 3 h (^{1}H NMR monitoring), the crude reaction was quenched with a mixture of H_2O and ice (600 g) and the organic layer was separated. The aqueous phase was then extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. After solvent evaporation, the crude reaction mixture was crystallized from AcOEt/hexane (15/30 mL) giving a mixture of *exo*-**3** and *endo*-**4** (15.4 g, 87%, 70:30) that was used for further experimentation without further purification. The mixture of *exo*-**3** and *endo*-**4** can be separated by chromatography as described.[8]

Synthesis of Esters 5a, 6a. The mixture of compounds **3**, **4** (15.4 g, 47.1 mol), obtained as reported above, was dissolved in EtOH (160 mL). Bis-(dibutylchlorotin)oxide (1.3 g, 2.35 mol) was added, and the mixture was refluxed for 3 h (TLC using AcOEt/*n*hexane, 1:1) after which the catalyst was filtered and the solvent evaporated. The crude reaction mixture was crystallized from AcOEt/hexane (10/40 mL) giving a mixture of esters *exo*-**5a** and *endo*-**6a** (17.2 g, 98%). The mixture of *exo*-**5a** and *endo*-**6a** can be separated by chromatography as described.[10]

Synthesis of Norbornanes 13, 14. A mixture of esters **5a**, **6a** (373 mg, 1 mmol) or the pure *exo*-**5a** (1.12, 3 mmol) or *endo*-***6a*** (750 mg, 2 mmol) suspended in EtOH (30 mL x 1 mmol of reagent) was reduced under hydrogen using Pd/C (10%, 107 mg, 0.1 mmol x 1 mmol of reagent) as the catalyst at 25 °C and 1 atm. After 2 h (^{1}H NMR monitoring), the catalyst was filtered and the solvent was eliminated. Compounds **13** and **14** were obtained in quantitative yield.

Ethyl (1*R,2*R**,3*S**,4*S**)-2-Benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]eptane-2-carboxylate *exo*-13:** mp 98 °C (AcOEt/hexane); IR ν_{max} 3405, 1734, 1656 cm^{-1}; ^{1}H NMR δ 7.84−7.43 (m, 5 H), 7.00 (s, 1 H, exch.), 5.05 (d, J = 4.0 Hz, 1 H), 4.32−4.16 (m, 4 H), 3.28 (bs, 1 H), 2.63 (bs, 1 H), 1.96 (d, J = 11.7 Hz, 1 H), 1.66−1.40 (m, 5 H), 1.35 (t, J = 6.9 Hz, 3 H), 1.23 (t, J = 7.3 Hz, 3 H); ^{13}C NMR δ 14.3, 14.4, 19.7, 23.9, 34.3, 39.9, 44.1, 61.7, 62.9, 64.9, 78.9, 127.3, 128.9, 132.0, 134.1, 153.9, 167.3, 172.3. Anal. Calcd: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.43; H, 6.91; N, 3.45.

Ethyl (1*R,2*S**,3*R**,4*S**)-2-Benzoylamino-3-ethoxycarbonyloxy-bicyclo[2.2.1]eptane-2-carboxylate *endo*-14:** mp 134 °C (AcOEt/hexane); IR ν_{max} 3405, 1734, 1656 cm^{-1}; ^{1}H NMR δ 7.77−7.39 (m, 5 H), 6.19 (s, 1 H, exch.), 5.68 (d, J = 1.5 Hz, 1 H), 4.32−4.02 (two m, 4 H), 2.55−2.40 (m, 2 H), 2.00 (d, J = 10.7 Hz, 1 H), 1.65−1.34 (m, 4 H), 1.26 (t, J = 7.0 Hz, 3 H), 1.15 (t, J = 7.4 Hz, 3 H); ^{13}C NMR δ 14.3, 14.4, 23.3, 24.1, 36.3, 43.3, 46.4, 61.6, 64.0, 69.6, 80.3, 127.3, 128.7, 131.8, 134.1, 154.3, 167.9, 170.9. Anal. Calcd: C, 63.99; H, 6.71; N, 3.73. Found: C, 63.43; H, 6.91; N, 3.45.

Synthesis of Methyl Esters 11, 12. A mixture of hydroxy-acids *exo*-**9** and *endo*-**10**[8] (1.1 g, 4 mmol) or pure *exo*-**9** (546 mg, 2 mmol) was dissolved in CH_2Cl_2 (6 mL x 2 mmol of reagent), and the solution was cooled at −10 °C. A solution of CH_2N_2 in ether was added dropwise until the starting material disappeared (TLC using CH_2Cl_2/Et_2O, 2:1). After solvent evaporation, a mixture of methyl esters **11, 12** (1.2 g, 100%) or pure *exo*-**11** (0.6 g, 100%) was obtained.

Methyl (1*S,2*R**,3*S**,4*R**)-2-Benzoylamino-3-hydroxy-bicyclo[2.2.1]ept-5-ene-2-carboxylate *exo*-11:** mp 170 °C (CH_2Cl_2/Et_2O); IR ν_{max} 3350, 3150,1720, 1620 cm^{-1}; ^{1}H NMR δ 7.88−7.39 (m, 5 H), 6.90 (s, 1 H, exch.), 6.39−6.35, 6.30−6.26 (two m, 2 H), 4.73 (dd, J = 5.5, 3.7 Hz, 1 H), 3.76 (s, 3 H), 3.72 (bs, 1 H), 3.07 (bs, 1 H), 2.57 (d, J = 5.5 Hz, 1 H, exch.), 1.84, 1.64 (AB system, J = 9.8 Hz, 2 H); ^{13}C NMR δ 44.1, 47.9, 49.6, 52.8, 64.9, 77.6, 127.3, 128.7, 131.9, 133.9, 136.4, 167.2, 174.4. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.79; H, 5.92; N, 4.78.

Methyl (1*S,2*S**,3*R**,4*R**)-2-Benzoylamino-3-hydroxy-bicyclo[2.2.1]ept-5-ene-2-carboxylate *endo*-12:** mp 188 °C (*i*-PrOH); IR ν_{max} 3350, 3150, 1720, 1620 cm^{-1}; ^{1}H NMR δ 7.84−7.37 (m, 5 H), 7.62 (s, 1 H, exch.), 6.33−6.28, 6.11−6.07 (two m, 2 H), 4.17 (bs, 1 H + 1 H exch.), 3.66 (s, 3 H), 3.33 (bs, 1 H), 2.76 (bs, 1 H), 2.00, 1.70 (AB system, J = 9.5 Hz, 2 H); ^{13}C NMR δ 45.5, 49.1, 49.6, 52.5, 65.3, 76.4, 127.4, 128.8, 132.0, 134.1, 134.5, 137.9, 167.5, 173.3. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.80; H, 5.93; N, 4.85.

Synthesis of Compounds 15a,b and 16b. Method A. A mixture of *exo*-**13** (1.12 g, 3 mmol) and lyophilized Na_2CO_3 (560 mg, 5.28 mmol) in EtOH (50 mL) was stirred at room temperature for 24 h (TLC: CH_2Cl_2/Et_2O, 2:1). The Na_2CO_3 was filtered over a Celite column and the alcohol was evaporated. Ester *exo*-**15a** was obtained and crystallized (900 mg, 99%). **Method B.** A mixture of esters **11**, **12** (3.15 g, 11 mmol) or pure *exo*-**11** (287 mg, 1 mmol) or *endo*-**12** (287 mg, 1 mmol) suspended in MeOH (10 mL x 1 mmol of reagent) was reduced under hydrogen using Pd/C (10%, 107 mg, 0.1 mmol x 1 mmol of reagent) as the catalyst at 25 °C and 1 atm. After 2 h (^{1}H NMR monitoring), the catalyst was filtered and the solvent was eliminated. Diastereomeric compounds from the *exo*/*endo* mixture can be partially separated by flash column chromatography on silica gel (230−400 mesh ASTM; CH_2Cl_2/AcOEt, 20:1). In a typical procedure, compounds **15b**, **16b** (289 mg) were separated giving two fractions: the first fraction contained *exo*-**15b** (111 mg, 40%); the second contained a mixture of *exo*-**15b** and *endo*-**16b** (126 mg, 46%).

Ethyl (1*R,2*R**,3*S**,4*S**)-2-Benzoylamino-3-hydroxy-bicyclo[2.2.1]eptane-2-carboxylate *exo*-15a:** mp 127 °C (AcOEt/Et_2O); IR ν_{max} 3350, 3150,1720, 1640 cm^{-1}; ^{1}H NMR δ 7.85−7.41 (m, 5 H), 7.33 (s, 1 H, exch.), 4.31−4.12 (m, 3 H), 3.17 (bs, 1 H), 2.96 (d, J = 4.7 Hz, 1 H, exch.), 2.41 (bs, 1 H), 1.86−1.62 (m, 2 H), 1.55−1.32 (m, 4 H), 1.23 (t, J = 7.3 Hz, 3 H). ^{13}C NMR δ 14.4, 18.8, 24.1, 34.3, 41.7, 43.9, 61.5, 62.9, 75.3, 97.2, 127.3, 128.8, 131.9, 134.3, 167.5, 174.0. Anal. Calcd: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.33; H, 6.51; N, 4.70.

Methyl (1*R,2*R**,3*S**,4*S**)-2-Benzoylamino-3-hydroxy-bicyclo[2.2.1]eptane-2-carboxylate *exo*-15b:** mp 196 °C (CH_2Cl_2); IR ν_{max} 3350, 3150,1720, 1640 cm^{-1}; ^{1}H NMR δ 7.86−7.30 (m, 6 H), 4.26 (d, J = 4.7 Hz, 1 H), 3.73 (s, 3 H), 3.17 (bs, 1 H), 3.00 (d, J = 4.7 Hz, 1 H, exch.), 2.41 (bs, 1 H), 1.85−1.62 (m, 2 H), 1.50−1.30 (m, 4 H); ^{13}C NMR δ 18.7, 23.9, 34.2, 41.6, 43.8, 52.5, 62.8, 75.1, 127.2, 128.7, 131.8, 133.9, 167.3, 174.3. $M^{+\cdot}$ (289). Anal. Calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.33; H, 6.51; N, 4.70.

Methyl (1*R,2*S**,3*R**,4*S**)-2-Benzoylamino-3-hydroxy-bicyclo[2.2.1]eptane-2-carboxylate *endo*-16b:** mp 197 °C (MeCN); IR ν_{max} 3345, 3150,1723, 1640 cm^{-1}; ^{1}H NMR δ 7.83−7.42 (m, 5 H), 6.42 (s, 1 H, exch.), 4.77 (d, J = 1.5 Hz, 1 H), 3.75 (s, 3 H), 2.80 (s, 1 H, exch.), 2.39 (bs, 2 H), 2.11 (d, J10.7, 1 H), 1.70−1.10 (m, 5 H); ^{13}C NMR δ 24.1, 29.9, 36.2, 44.5, 46.8, 52.6, 71.1, 78.4, 127.5, 128.8, 132.3, 133.5, 170.1, 172.5. Anal. Calcd: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.30; H, 6.48; N, 4.69.

Synthesis of Compounds 17, 18. Compound *exo*-**15b** (1.7 g, 6 mmol) or *endo*-**16b** (289 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL x 1 mmol of reagent), and under nitrogen was added PCC (1.3 g, 6 mmol x 1 mmol of reagent). The solution was stirred at room temperature for 2 h (TLC using cyclohexane/AcOEt, 1:1). The reaction mixture was filtered through a silica gel column (cyclohexane/AcOEt, 1:1). Keto compound (*exo*-**17**, 1.6 g, 95%; *endo*-**18**, 115 mg, 40%) was obtained and crystallized.

Methyl (1*R,2*R**,4*S**)-2-Benzoylamino-3-oxo-bicyclo-[2.2.1]eptane-2-carboxylate *exo*-17:** mp 202 °C (cyclohexane/AcOEt); IR ν_{max} 3320, 1720, 1700, 1640 cm^{-1}; ^{1}H NMR δ

7.84−7.42 (m, 5 H), 6.72 (s, 1 H, exch.), 3.74 (s, 3 H), 2.82 (d, J = 5.1 Hz, 1 H), 2.51, 1.85 (AB system, J = 11.3 Hz, 2 H), 2.09−1.94 (m, 1 H), 1.78−1.52 (m, 4 H); ^{13}C NMR δ 21.9, 27.5, 34.7, 44.2, 48.1, 53.2, 71.8, 127.3, 128.7, 132.2, 133.3, 166.8, 167.9, 209.9. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.80; H, 5.92; N, 4.61.

Methyl (1*R,2*S**,4*S**)-2-Benzoylamino-3-oxo-bicyclo-[2.2.1]eptane-2-carboxylate *endo*-18:** mp 205 °C (AcOEt); IR ν_{max} 3320, 1720, 1700, 1640 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.69 (s, 1 H, exch.), 7.84−7.46 (m, 5 H), 3.64 (s, 3 H), 2.85 (bs,1 H), 2.61 (d,J = 3.7, 1 H), 2.15 (d, J = 10.7 Hz, 1 H), 2.03−1.40 (m, 5 H); ^{13}C NMR δ 23.4, 23.7, 34.5, 44.9, 49.7, 52.5, 68.4, 128.4, 128.9, 132.3, 134.3, 167.1, 170.2, 207.6. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.83; H, 5.94; N, 4.81.

General Procedure for the Retro-Aldol Reaction of Carbonates 3, 5a, 6a, and 5c. Cycloadduct *exo*-**3** or pure ester **5a**, **5c**, **6a** (1 mmol) in alcohol (**3**, MeOH; **5a**, **6a**, and **5c**, EtOH; 20 mL) was heated at reflux after which lyophilized Na_2CO_3 (187 mg, 1.76 mmol) was added. The heating was continued for the following times: *exo*-**3**, 20 min; *exo*-**5a**, 1 h; *endo*-**6a**, 2 h; *exo*-**5c**, 8 h (TLC using CH_2Cl_2/Et_2O, 2:1). Then, residual Na_2CO_3 was removed by filtration through a Celite column, and the filtrate was evaporated to dryness. A mixture of aldehydes **19** and **20** was obtained in a 1:1 ratio (from **3**, **19b/20b**, 198 mg, 69%; from *exo*-**5a**, **19a/20a**, 246 mg, 82%; from *endo*-**6a**, **19a/20a**, 240 mg, 80%; from **5c**, **19c/20c**, 74%) and analyzed by HPLC using a Hypersil column (**19a**,**b/20a**,**b**: 5 μ; 250 mm × 4.6 mm; *n*hexane/AcOEt, 4:1; T = 30 °C; flow = 1 mL/min; λ = 254). It is possible to separate the diastereomeric aldehydes by column flash chromatography on silica gel (230−400 mesh ASTM; **19/20b** *n*hexane/AcOEt, 4:1; **19/20c** cyclohexane/AcOEt, 4:1). In a typical procedure, compounds **19b**, **20b** (110 mg) were separated on a column (1.5 × 20 cm; flow = 20 mL/min), which gave a first fraction containing only **19b** (40 mg), a second fraction containing a mixture of diastereomers **19b**, **20b** (20 mg), and a third fraction containing pure **20b** (45 mg).

Ethyl Benzoylamino-(3′-formylcyclopent-3′-enyl)-acetates 19a/20a (Mixture of Compounds): ^{1}H NMR δ 9.76, 9.75 (two s, 1 + 1 H), 7.82−7.32 (m, 5 + 5 H), 6.95−6.70 (m, 4 H), 5.00−4.88 (m, 1+1 H), 4.38−4.20 (m, 2+2 H), 3.35−2.40 (m, 5+5 H), 1.20−1.08 (two t, 3 + 3 H). Anal. Calcd: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.50; H, 6.43; N, 4.52.

Methyl (1*R,1′*R**)-Benzoylamino-(3′-formylcyclopent-3′-enyl)-acetate 19b:** mp 129 °C (Et_2O/*n*pentane); IR ν_{max} 3336, 1742, 1672, 1640 cm^{-1}; ^{1}H NMR δ 9.75 (s, 1 H), 7.82−7.43 (m, 5 H), 6.82 (s, 1 H), 6.69 (d, J = 8.5 Hz, 1 H, exch.), 5.00 (dd, J = 8.5, 5.7 Hz, 1 H), 3.79 (s, 3 H), 3.30−2.98 (m, 1 H), 2.80−2.40 (m, 4 H); ^{13}C NMR δ 30.6, 36.6, 40.4, 52.7, 54.9, 127.2, 128.7, 132.0, 133.7, 146.1, 151.2, 167.5, 172.1, 189.3. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.00; H, 6.01; N, 4.95.

Methyl (1*S,1′*R**)-Benzoylamino-(3′-formylcyclopent-3′-enyl)-acetate 20b:** mp 126 °C (Et_2O); IR ν_{max} 3344, 1723, 1675, 1661 cm^{-1}; ^{1}H NMR δ 9.76 (s, 1 H), 7.82−7.44 (m, 5 H), 6.82 (s, 1 H), 6.70 (d, J = 7.3 Hz, 1 H, exch.), 4.94 (dd, J = 8.0, 7.3 Hz, 1 H), 3.80 (s, 3 H), 3.03−2.88 (m, 1 H), 2.79−2.43 (m, 4 H); ^{13}C NMR δ 31.3, 36.4, 40.8, 52.7, 55.4, 127.1, 128.7, 132.0, 133.8, 146.5, 150.4, 167.3, 172.2, 189.3. Anal. Calcd: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.00; H, 5.99; N, 4.81.

(−)-Menthyl (1*R*,1′*R*)-Benzoylamino-(3′-formylcyclopent-3′-enyl)-acetate 19c: mp 110 °C (Et_2O/*n*-pentane); $[\alpha]^{25}_D$ = −52 (*c* 1, $CHCl_3$); IR ν_{max} 3344, 1727, 1679, 1640 cm^{-1}; ^{1}H NMR δ 9.74 (s, 1 H), 7.81−7.44 (m, 5 H), 6.81 (s, 1 H), 6.70 (d, J = 8.5 Hz, 1 H, exch.), 4.99 (dd, J = 8.5, 4.7 Hz, 1 H), 4.81−4.73 (m, 1 H), 3.20−3.00 (m, 1 H), 3.00−2.40 (m, 4 H), 2.10−0.75 (m, 18 H); ^{13}C NMR δ 16.1, 21.2, 22.3, 23.3, 26.5, 30.4, 31.8, 34.5, 37.3, 40.7, 41.1, 47.3, 55.5, 76.6, 127.4, 129.1, 132.3, 134.2, 146.3, 151.8, 168.0, 171.5, 189.6. Anal. Calcd: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.73; H, 8.15; N, 3.29.

(−)-Menthyl (1*S*,1′*R*)-Benzoylamino-(3′-formylcyclopent-3′-enyl)-acetate 20c: mp 129 °C (Et_2O); $[\alpha]^{25}_D$ = −18 (*c* 1, $CHCl_3$); IR ν_{max} 3344, 1731, 1679, 1661 cm^{-1}; ^{1}H NMR δ 9.75 (s, 1 H), 7.83−7.43 (m, 5 H), 6.80 (bs, 2 H), 4.93 (dd, J = 8.0, 6.8 Hz, 1 H), 4.85−4.72 (m, 1 H), 3.10−2.90 (m, 1 H), 2.90−2.45 (m, 4 H) 2.10−0.73 (m, 18 H); ^{13}C NMR δ 16.3, 20.7, 22.0, 23.5, 26.3, 31.4, 31.5, 34.1, 36.1, 40.8, 41.0, 47.0, 55.2, 76.3, 127.1, 128.7, 131.9, 134.1, 146.7, 150.2, 167.2, 171.3, 189.1. Anal. Calcd: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.80; H, 8.12; N, 3.33.

General Procedure for the Retro-Claisen Reaction of Ketones 17, 18. Method a. A mixture of ketones **17**, **18** or pure *exo*-**17** (574 mg, 2 mmol) was dissolved in pyridine (6 mL) and H_2O (2 mL). The reaction mixture was heated at reflux for 3 h (TLC using CH_2Cl_2/Et_2O, 2:1). The solvent was removed, and the residue was taken up in a HCl solution (10%, 20 mL) that was then extracted with AcOEt (3 × 15 mL). The organic layer was separated and dried over Na_2SO_4, giving a mixture of the two diastereomeric acids **21**, **22** (1:1, 508 mg, 83%). **Method b.** Ketone *exo*-**17** (574 mg, 2 mmol) was dissolved in acetone (56 mL) and DMF (5.6 mL). The solution was heated at reflux and $NaHCO_3$ (168 mg, 2 mmol) was added. After 3 h, the solvent was evaporated; the mixture was taken up in aqueous HCl (10%, 30 mL), and the solution was extracted with a THF/AcOEt mixture (1:1, 3 × 15 mL). The organic layer was washed with brine (2 × 15 mL) and dried over Na_2SO_4, giving a mixture of **21** and **22** (1:2, 458 mg, 75%). The crystallization of the mixture of acids from CH_2Cl_2/*i*Pr_2O gave pure diastereomer **22** (230 mg). It is possible to separate **21** from **22** by column chromatography (CH_2Cl_2/Et_2O, 10:1).

***1S*,3R*,1′R**-3-(Benzoylamino-methoxycarbonylmethyl)cyclopentanecarboxylic Acid 21:** oil; IR ν_{max} 3340, 1732, 1700, 1668 cm^{-1}; ^{1}H NMR δ 7.89−7.40 (m, 5 H), 7.12 (d, J = 8.0 Hz, 1 H, exch.), 4.91 (dd, J = 8.0 Hz, 5.2 H, 1 H), 3.79 (s, 3 H), 3.00−2.82 (m, 1 H), 2.75−2.55 (m, 1 H), 2.10−1.80 (m, 4 H), 1.80−1.70 (m, 1 H); ^{13}C NMR δ 28.7, 30.3, 30.9, 42.2, 43.3, 52.8, 55.2, 127.6, 128.9, 132.2, 134.1, 168.3, 173.1, 182.0. Anal. Calcd: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.87; H, 6.34; N, 4.50.

***1S*,3R*,1′S**-3-(Benzoylamino-methoxycarbonylmethyl)cyclopentanecarboxylic Acid 22:** mp 135 °C; IR ν_{max} 3340, 1730, 1700, 1665 cm^{-1}; ^{1}H NMR δ 7.84−7.42 (m, 5 H), 6.89 (d, J = 7.3 Hz, 1 H, exch.), 4.88 (dd, J = 7.3, 7.0 Hz, 1 H), 3.79 (s, 3 H), 2.90−2.86 (m, 1 H), 2.58−2.50 (m, 1 H), 2.20−2.10 (m, 1 H), 2.00−1.60 (m, 5 H); ^{13}C NMR δ 27.9, 29.5, 32.7, 42.8, 43.5, 52.8, 55.3, 127.6, 128.9, 132.2, 134.2, 168.1, 173.0, 181.7. Anal. Calcd: C, 62.94; H, 6.27; N, 4.59. Found: C, 70.00; H, 6.31; N, 4.64.

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Supporting Information Available: General experimental and X-ray data for compound **20c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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