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Functionalized Azabicycloalkane Amino Acids by Nitrone 1,3-Dipolar Intramolecular Cycloaddition

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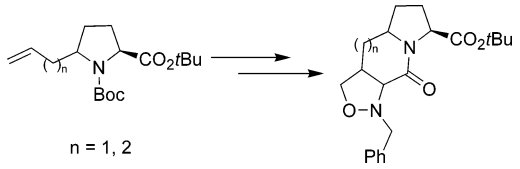

An efficient and operationally simple method for the synthesis of functionalized azaoxobicyclo-[*X*.3.0]alkane amino acids has been devised. The key step is an intramolecular nitrone cycloaddition on 5-allyl- or 5-homoallylproline that was found to be completely regio- and stereoselective.

Introduction

Biologically active peptides are involved in a great number of physiological processes through their interaction with receptors and enzymes. However, peptides are not ideal drug candidates due to their low metabolic stability toward endogenous proteases, poor oral bioavailability, rapid excretion, and lack of selectivity toward a specific receptor, due to conformational flexibility. To overcome these difficulties the synthesis of so-called peptidomimetic molecules is a very active and productive field of research in medicinal chemistry.[1] Since reverse-turn motifs are implicated as recognition elements in a variety of biological interactions, much effort has been focused on the design and synthesis of small constrained mimetics of turn structures.[1,2] In this regard, of particular interest is the replacement of reverse-turn dipeptide motifs with constrained molecules that reproduce their conformational features, i.e., peptide secondary structures. Azabicyclo[*X*.*Y*.0]alkane amino acids are particularly attractive constrained dipeptide mimics because of their ability to serve as conformationally fixed surrogates of peptide turn secondary structures.[3]

The possibility of functionalizing azabicycloalkane amino acids with lipophilic or hydrophilic appendages is very attractive because such appendages could improve peptide-receptor affinity by interacting with hydrophobic or hydrophilic pockets. Furthermore, diversification of bicyclic lactams by tethering of different pharmacophoric groups may generate library members exhibiting different biological activity. Thus, we set about to synthesize azabicyclo[*X*.*Y*.0]alkanes that possess heteroatom-substituted side chains. Although many reports on the synthesis of bicyclic lactams can be found in the literature[4] only a few describe the preparation of azabicyclo-[*X*.*Y*.0]alkanes bearing functionalized side chains.[5] Recently, we reported our own research efforts in this field (Figure 1).[6] Our synthetic approaches were based on a Horner−Emmons methodology for the synthesis of both 6,5- or 7,5-fused bicyclic lactams substituted at the proline moiety[6a] (Figure 1, type **I**) or an RCM strategy

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(1) See, for example: (a) Gante, J. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1699; (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem*. **1993**, *36*, 3039; (c) Horwell, D. C. *Bioorg. Med. Chem. Lett*. **1993**, *3*, 797; (d) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 1244; (e) Morgan, B. A.; Gainor, J. A. *Annu. Rep. Med. Chem*. **1989**, *24*, 243.

(2) Kahn, M. Ed. Peptide Secondary Structure Mimetics. *Tetrahedron Symposia-in-Print No. 50* **1993**, *49*, 3433 and references cited therein.

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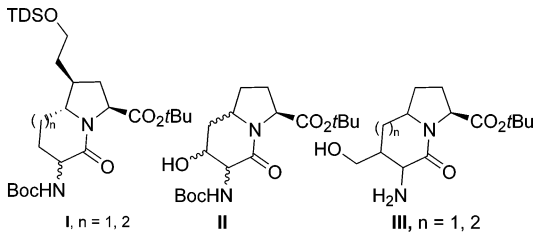


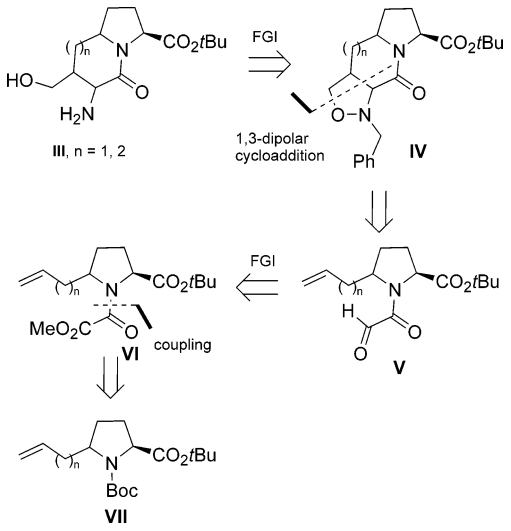
FIGURE 1. Functionalized azabicycloalkane amino acids.

for the synthesis of similar 7,5-fused systems (Figure 1, type **I**).[6b] Furthermore, an aldolic strategy has been applied for the synthesis of heterosubstituted 6,5-fused bicyclic lactams at the lactam ring (Figure 1, type **II**).[6c] However, the high number of steps, or the lack of selectivity of these methods, forced us to investigate new synthetic routes for the preparation of functionalized azabicyclo[*X*.*Y*.0]alkanes. For this purpose, we devised a new synthetic approach based on a intramolecular nitrone cycloaddition (INC) reaction for the construction of lactams of type **III** (Figure 1).

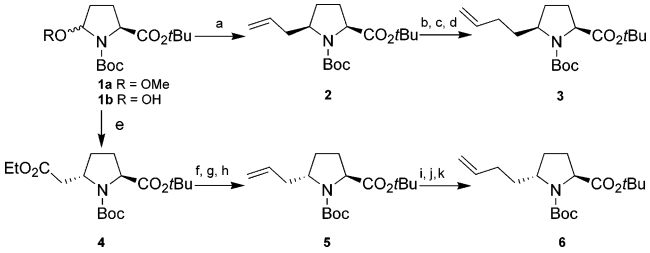
The intramolecular nitrone cycloaddition reaction with olefins (INC) finds broad applications in organic synthesis. The isoxazolidines formed from this reaction have a labile N−O bond that is easily converted into various functional groups. These sequences have been utilized as key steps for the stereoselective synthesis of highly functionalized pyrrolidines and piperidines that have been applied to the synthesis of biologically active natural products.[7]

In this paper, we report our studies toward the synthesis of functionalized azabicyclo[*X*.*Y*.0]alkanes using the intramolecular cycloaddition reactions of nitrones derived from suitably protected pyrrolidines.

SCHEME 1. Retrosynthetic Scheme for the Synthesis of Functionalized Azabicycloalkane Amino Acids of Type III.



SCHEME 2. Synthesis of the *cis*- and *trans*-5-Substituted Prolines[a]



[a] From **1a**: (a) allyltributyltin, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, cis/trans 66:34, 80%; (b) 9-BBN, H_2O_2, 95%; (c) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −60 °C, 89%; (d) Ph_3PCH_3Br, BuLi, THF, −78 °C, 90%. From **1b**: (e) triethyl phosphonoacetate, KH, DMF, 92%, trans/cis 90:10; (f) $LiBH_4$, Et_2O, −10 °C, 73%; (g) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 98%; (h) Ph_3PCH_3Br, BuLi, THF, −78C, 90%; (i) 9-BBN, H_2O_2, 92%; (j) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78 °C, 95%; (k) Ph_3PCH_3Br, BuLi, THF, −78C, 80%.

Results and Discussion

Our retrosynthetic analysis of type **III** lactams is reported in Scheme 1.

A suitably protected precursor for the 1,3-dipolar cycloaddition is the glioxylamide derivative **V** that, via functional group interconversion, could be derived from the oxalamide precursors **VI** easily obtained from the known protected 5-allyl- or homoallylprolines **VII**.[4n]

As mentioned above, the synthetic methodologies for the preparation of the 5-substituted prolines **VII** are already well defined. However, if the prolines **2**, **3**, and **5** can be easily obtained from **1**,[4n] the reported synthesis of *trans*-homoallylproline **6** is longer and tedious (Scheme 2).[4n]

With the aim of simplifying the synthetic sequence for the preparation of **6**, a direct homoallylation of **1** was attempted (Scheme 3). According to the literature[8] and our own experience on similar substrates,[9] a boron trifluoride-mediated cuprate addition to the hemiaminal **1** could generate the trans adduct **6** stereoselectively. In

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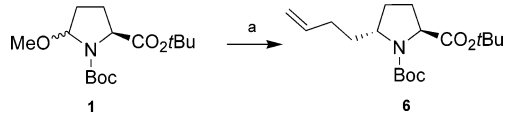
(7) (a) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; pp 83−168. (b) Padwa, A.; Schoffstall, A. M. In *Advances in Cycloaddition*; Curran, D., Ed.; JAI Press: Greenwich, CT, 1990; pp 2−28; (c) Denmark, S. E.; Thorarsensen, A. *Chem. Rev*. **1996**, *96*, 137. (d) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Tetrahedron Organic Chemistry Series; Pergamon Press: Oxford, 1990; Vol. 8, pp 296−313.; (e) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863.

(8) Chiesa, M. V.; Manzoni, L.; C. Scolastico, L. *Synlett* **1996**, 441.

SCHEME 3. Preparation of *trans*-5-Homoallylproline 6 via Direct Butenylation of the Hemiaminal 1[a]



1 6

[a] Key: (a) butenylMgBr, CuBr·Me_2S, BF_3·Et_2O, THF, 95%, trans/cis 95:5.

fact, when the known hemiaminal **1**[10] was treated with butenylmagnesium bromide, in the presence of CuBr·Me_2S and boron trifluoride, the *trans*-homoallylproline **6** was obtained in 95% yield and 95:5 diastereoisomeric ratio. To the best of our knowledge, this procedure represents the first example of direct butenylation of a hemiaminal to afford the *trans*-5-homoallylproline.

With the starting materials in hand, we began our synthetic procedure for the synthesis of 1,3-dipolar cycloaddition precursors.

Selective removal of the *tert*-butoxycarbonyl protecting group (Scheme 4a) from the *cis*-allylproline **2** with $HClO_4$ in *t*BuOAc gave the corresponding amine that was neutralized by treatment with $NaHCO_3$. The amine was then treated with methyl chloroxaacetate (MeO_2CCOCl) in the presence of Amberlyst A-21 affording the ester **7** in 76% yield. Compound **7** was converted to the aldehyde **9** by $LiBH_4$ reduction to the corresponding alcohol **8** followed by Swern oxidation (Scheme 4a). With the same synthetic sequence, the aldehyde **12** was obtained from the *cis*-5-homoallylproline **3** (Scheme 4b), and the *trans*-aldehydes **15** and **18** were obtained from **5** and **6**, respectively (Scheme 5).

The nitrones were generated by treatment of the appropriate aldehyde (**9**, **12**, **15**, and **18**) with BnNHOH·HCl in the presence of $NaHCO_3$ and in 9:1 ethanol/H_2O as solvent and underwent cycloaddition in situ. The 1,3-dipolar cycloaddition reaction was found to be highly regio- and stereoselective for precursors **9**, **12**, and **15**, affording the tricyclic lactones **19**−**21** as single isomer (Schemes 4 and 5). In contrast, **18**, under the same reaction conditions, gave a 2:1 diastereoisomeric mixture of **22a**,**b**. Nevertheless, compound **22a** was selectively obtained when the reaction was performed in 2:1 toluene/H_2O (Scheme 5). Hence, under the appropriate conditions, the conversion of **18** to the isoxazolidine **22a** could be effected with total stereocontrol.

The structural assignment of the tricyclic cycloadducts, and of the regio- and stereochemistry of the nitrone 1,3-dipolar cycloaddition, was achieved by extensive mono- and bidimensional NMR analysis. The regioselectivity of the process was easily established by the ^1H and ^{13}C NMR spectral characteristics of the products. In compounds **19** and **21** (Figure 2), the appearance of a doublet for 8a-H at δ 3.22 and δ 3.36 ppm, respectively, correlated to a methine carbon signal at δ 64.1 and δ 65.0 ppm, respectively (8a-C), is a good indication of the formation of the fused C-4-substituted isoxazolidine skeleton de-

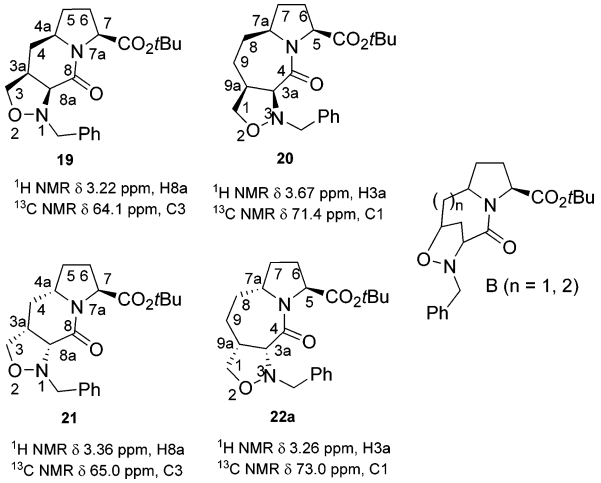


FIGURE 2. Assignment of the regiochemistry by NMR chemical shift analysis.

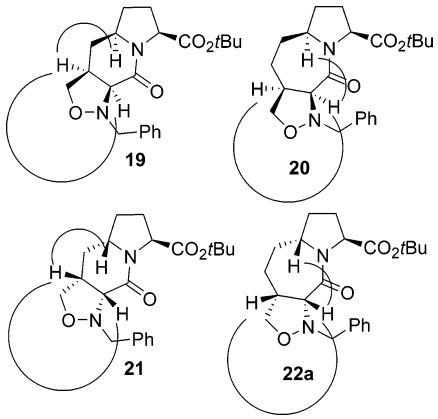


FIGURE 3. Diagnostic NOE contacts in the spectra of **19**−**22a**.

picted in Figure 2. No signals for the bridged C-5 substituted isoxazolidines type **B** have been observed.

The ^1H NMR spectra of **19** and **21** (Figure 2) showed a coupling constant of 9.0−10.0 Hz between 3a-H and 8a-H suggesting a dihedral angle near 0° between the two protons and hence a cis stereochemistry. This tentative assignment was further confirmed by NOESY experiments (Figure 3): in compounds **19** and **21**, diagnostic cross-peaks between 3a-H and 8a-H were observed, assigning unequivocally the cis configuration between C3a and C8a. Furthermore, in compounds **19** and **21** a NOE cross-peak between the protons H3a−H4a allowed us to assign the configuration at C3a and C8a as 8a*S*,3a*S* (in **19**) and 8a*R*,3a*R* (in **21**). Similar considerations led to the assignment of the regio- and stereochemistry of compounds **20** and **22a** (Figures 2 and 3).

The stereochemical outcome[11] of the nitrone 1,3-dipolar intramolecular cycloaddition has been investigated by means of a force field approach previously developed for evaluating the stereoselection in nitrone cycloadditions to chiral alkenes.[12] In this approach, the Macromodel[13]

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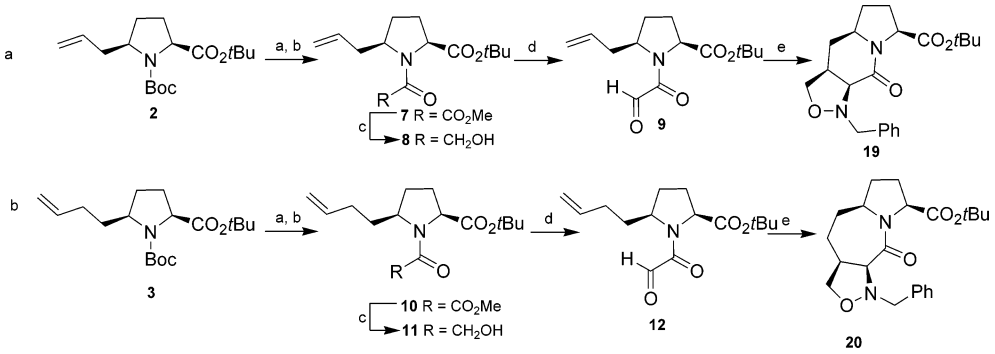
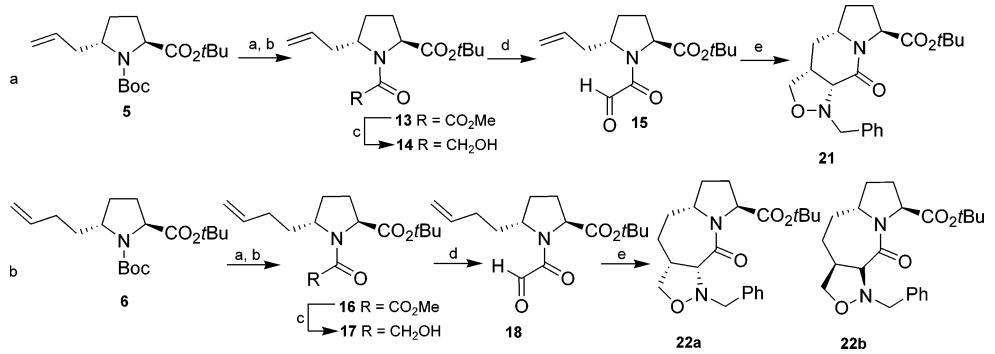
SCHEME 4. Synthesis of the *cis*-5-Substituted 1,3-Dipolar Precursors and 1,3-Dipolar Cycloadducts[a]



[a] Key: (a) tBuOAc, $HClO_4$; (b) methyl chloroxaacetate (MeO_2CCOCl), Amberlyst A-21, DCM, 76% (**7**), 79% (**10**) over two steps; (c) $LiBH_4$, THF, 75% (**8**), 76% (**11**); (d) Swern oxidation; (e) BnNHOH·HCl, $NaHCO_3$, ethanol/H_2O 9/1, 55% (**19**), 57% (**20**), over three steps.

SCHEME 5. Synthesis of the *trans*-5-Substituted 1,3-Dipolar Precursors and 1,3-Dipolar Cycloadducts[a]



[a] Key: (a) *t*BuOAc, $HClO_4$; (b) methyl chloroxaacetate, Amberlyst A-21, DCM, 76% (**13**), 80% (**16**) over two steps; (c) $LiBH_4$, THF, 84% (**14**), 90% (**17**); (d) Swern oxidation; (e) BnNHOH·HCl, $NaHCO_3$, ethanol/H_2O 9/1, 71% (**21**), BnNHOH·HCl, $NaHCO_3$, toluene/H_2O 55% (**22a**) over three steps.

MM2* force field[14] was parametrized on the basis of ab initio data within the frame of "Transition State Modeling".[12,15]

Within this approach, a simple model of the reaction TS is studied with ab initio (or semiempirical) methods, thus obtaining suitable parameters to be included in commonly used force fields. In this way, energy differences can be evaluated for diastereoisomeric transition structures, as is usually done for diastereoisomeric ground states. The set of parameters for nitrone *plus* alkene cycloaddition TS was developed by Raimondi et al.[12] and included as a substructure in the MacroModel V5.5 MM2* force field, thus allowing application of the usual conformational analysis techniques to the transition structures.

Conformational analysis of the diastereoisomeric transition structures (MC/EM procedure)[16] was performed considering both intramolecular *endo* and *exo* approaches of the dipolarophile to the *si* and *re* face of the nitrone in *cis*- and *trans*-5-allyl 1,3-dipolar precursors generated from **9** and **15**, for a total four diastereomeric TS. The different stereoselectivity obtained for the *cis*- and *trans*-5-allyl 1,3-dipolar precursors is well reproduced by the calculation. For the *cis*-5-allyl precursor the calculated transition structure corresponding to the *exo* attack of the dipolarophile to the nitrone *si* face and leading to the experimentally observed isomer **19** is favored by at least 1.4 kcal/mol over the other diastereoisomeric structures (Figure 4).[17]

Similarly, the calculated transition structure corresponding to the *endo* attack of the dipolarophile to the nitrone *re* face and leading to the experimentally observed isomer **21** is favored by 1.2 kcal/mol over the other diastereoisomeric structures in the case of *trans*-5-allyl precursor (Figure 5).[17]

Finally, the easy cleavage of the isoxazolidine ring was demonstrated in all compounds, as shown in Scheme 6. Thus, hydrogenolysis in methanol under standard condition (Pd on charcoal) gave the amino alcohols **23**−**26** in 90−99% yield. Moreover, the N−O bond can be selectively cleaved by SmI_2[18] to afford the corresponding

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(17) In Figures 4 and 5, only the lowest energy structures leading to the four possible diastereoisomers are shown. Other conformers differing in bicyclic lactam conformation and/or benzyl orientation are located by MC/EM conformational searches. Diastereoisomeric ratios have been evaluated in each case considering a Boltzmann distribution at 300 K of all conformers within 3 kcal/mol of the global minimum. The transition structures calculated from *cis*- and *trans*-5-allyl precursors leading to the experimentally observed isomers **19** and **21** are populated 90% and 75%, respectively, in qualitative agreement with the experimental results.

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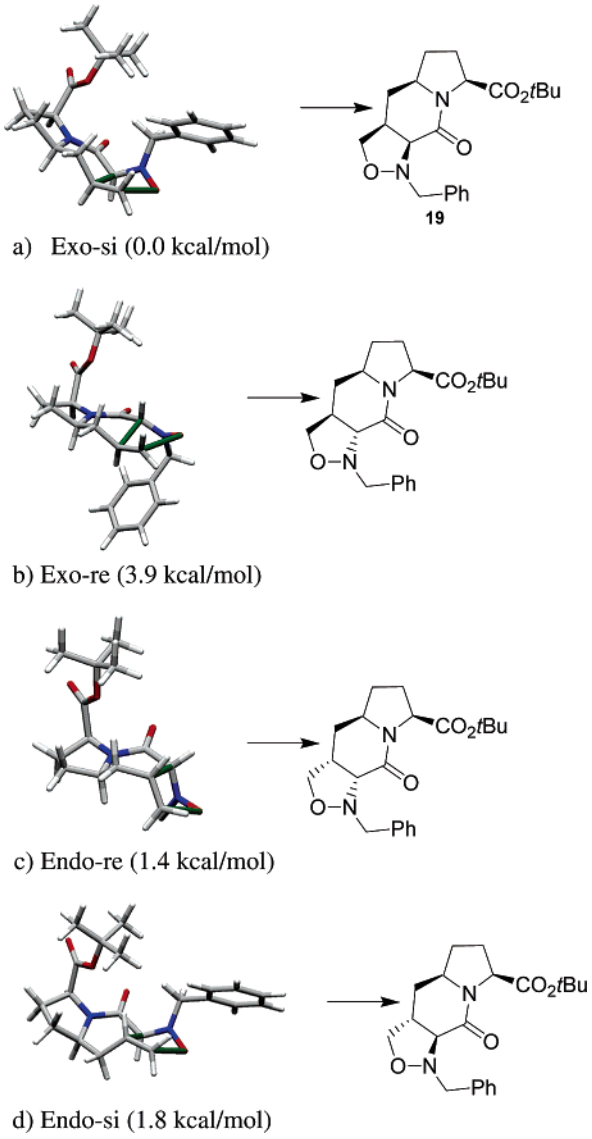


FIGURE 4. Lowest energy transition structures calculated for *cis*-5-allyl 1,3-dipolar precursor generated from **9**. Forming bonds are in dark green. In structure c, the benzyl group is omitted for clarity.

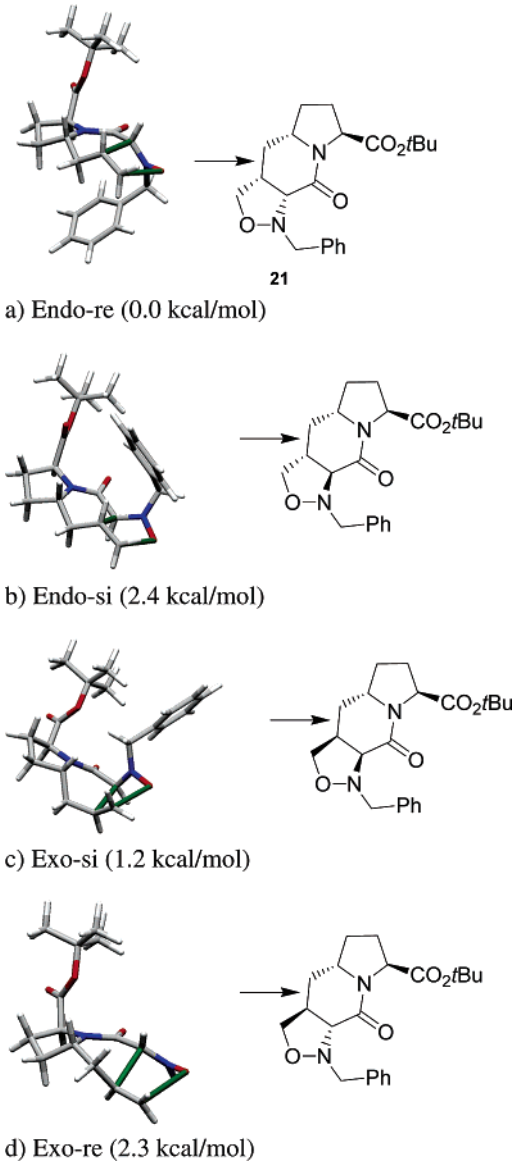


FIGURE 5. Lowest energy transition structures calculated for *trans*-5-allyl 1,3-dipolar precursor generated from **15**. Forming bonds are in dark green. In structure d, the benzyl group is omitted for clarity.

N-benzylamino alcohols **27**−**30** in good yields. These structures could be regarded as conformationally restricted substitutes for the homoSer-Pro dipeptide.

Conclusions

In conclusion, 5-allyl- and 5-homoallylproline nitrone cycloaddition has been established as an efficient and operationally simple method for the synthesis of functionalized azaoxobicyclo[*X*.3.0]alkane amino acids mimics of a homoSer-Pro dipeptide. It has also been demonstrated that the 1,3-dipolar nitrone cycloaddition reaction is completely regio- and stereoselective. Furthermore, a new method for the synthesis of 5-butenylproline has been individuated, based on the stereoselective addition of butenylmagnesium bromide on a suitable protected hemiaminal mediated by copper salts.

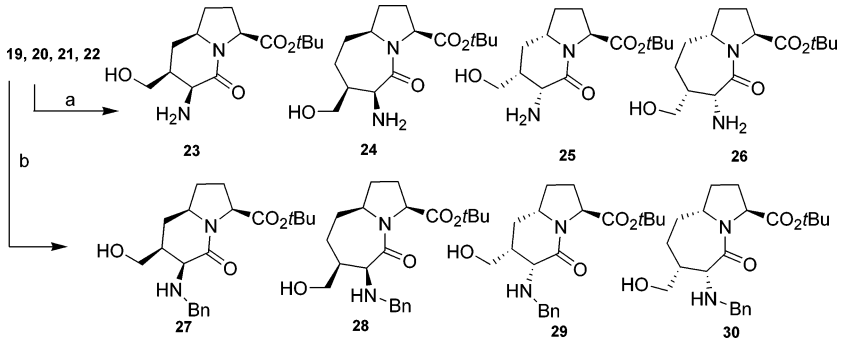
Experimental Section

Computational Methods. Molecular mechanics calculations were performed in vacuo using the MacroModel/Batchmin V5.5 package[13] and the MM2* force field,[14] augmented with the substructure for the nitrone *plus* alkene TS.[12] The torsional space of each diastereoisomer was randomly varied with the usage-directed Monte Carlo conformational search of Chang, Guida, and Still.[16] Ring-closure bonds were defined in the lactam and isoxazolidine rings of the tricyclic cycloadducts in formation. For each search, at least 1000 starting structures for each variable torsion angle were generated and minimized until the gradient was less than 0.05 kJ/(Å mol) using the truncated Newton conjugate gradient method[19] implemented in MacroModel. All unique conformations within 6 kcal/mol of the global minimum were stored.

(2*R*,5*R*)-5-But-3-enyl-pyrrolidine-1,2-dicarboxylic Acid Di-*tert*-butyl Ester 6. To a suspension of Mg (15.3 g, 629.1

(19) Ponder, J. W.; Richards, F. M. *J. Comput. Chem.* **1987**, *8*, 1016.

SCHEME 6. Cleavage of the Isoxazolidines[a]



[a] Key: (a) H_2, Pd−C, MeOH, 90−99%; (b) SmI_2, THF, 68−80%.

mmol) in dry THF (250 mL), under an argon atmosphere, was added a catalytic amount of I_2, and subsequently, 4-bromo-1-butene (26.6 mL, 262.13 mmol) was added dropwise to maintain a gentle reflux. After 1.5 h, the solution was slowly added via cannula to a vigorously stirred suspension of CuBr·DMS (43 g, 209.7 mmol) in dry THF (250 mL) at −78 °C. The resulting dark brown mixture was stirred for 45 min at −78 °C, and then $BF_3{\cdot}Et_2O$ (26.6 mL, 209.7 mmol) was added dropwise. After 30 min, a solution of **1** (15.6 g, 51.76 mmol) in dry THF (50 mL) was slowly added via cannula, and then the dark brown reaction mixture was allowed to warm at room temperature over 1 h. After reaction completion, a 1:1 mixture of saturated NH_4Cl/NH_4OH (800 mL) was added. The resulting mixture was vigorously stirred for 16 h and then extracted with diisopropyl ether (3 × 1 L). The organic phase was washed with a saturated solution of $NaHCO_3$ (300 mL), dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (hexane/EtOAc 95:5) to give **6** (95%) as a white solid in a 95:5 trans/cis diastereoisomeric ratio: mp = 74−75 °C; $[\alpha]^{22}_D$ = −68.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) (2:1 mixture of conformers) δ 1.24−1.4 (m, 1H, C*H*$_2$−CH_2−CH=CH_2), 1.43, 1.46 (2 s, 18H, C(C*H*$_3$)$_3$ *t*Bu and Boc), 1.66 (m 0.7H, *H*-4 major conformer), 1.78 (m, 0.3H, *H*-4 minor conformer), 1.85−2.24 (m, 4H, *H*-3, *H*-4, C*H*$_2$$CH_2$CH=$CH_2$), 2.24−2.38 (m, 1H, H-3 both conformers), 3.9 (m, 0.3H, *H*-5 minor conformer), 4.0 (m, 0.7H, *H*-5 major conformer), 4.12 (m, 0.7H, *H*-2 major conformer), 4.2 (m, 0.3H, *H*-2 minor conformer), 4.92−5.1 (m, 2H, CH_2CH_2CH=C*H*$_2$), 5.77−5.90 (m, 1H, CH_2-CH_2C*H*=CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 172.3, 172.2, 154.5, 153.9, 138.3, 138.1, 114.8, 114.6, 80.8, 79.6, 60.5, 57.9, 57.5, 34.0, 33.1, 31.0, 30.9, 28.7, 28.5, 28.4, 28.3, 28.1, 28.0, 27.7, 27.2; MS (FAB$^+$) *m/z* 326 [M + H]$^+$. Anal. Calcd for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.53; H, 9.48; N, 4.18.

General Procedure A. Acylation Reaction. To a solution of the allyl- or homoallylprolines **2**−**6** (0.292 mmol) in *t*BuOAc (2.9 mL), at 0 °C, was slowly added $HClO_4$ 70% (75 μL, 0.876 mmol). After 3 h, a saturated solution of $NaHCO_3$ was added, and the product was extracted with CH_2Cl_2. The organic phase, dried with Na_2SO_4, was evaporated under reduced pressure. The crude was dissolved in CH_2Cl_2 (2.9 mL), and Amberlyst A-21 was added until pH = 8. The mixture was subsequently cooled at −20 °C, and methyl chloroxaacetate (54 μL, 0.584 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1 h, then the suspension was filtered and washed with CH_2Cl_2 (15 mL). The organic phase was evaporated under reduced pressure, and the residue was purified by flash chromatography to give methyl esters **7**, **10**, **13**, or **16**.

(2*R*,5*S*)-5-Allyl-1-methoxyoxalylpyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 7. Compound **7** was prepared following the general procedure A. The crude was purified by flash chromatography (hexane/EtOAc 8:2) affording the pure product (76% over two steps) as white solid: mp = 55−56 °C; $[\alpha]^{22}_D$ = −35.3 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (1:1.5 mixture of conformers) δ 1.5 (s, 9H, C(C*H*$_3$)$_3$ both conformers), 1.78−1.89 (m, 0.6H, *H*-4 major conformer), 1.9−2.05 (m, 1H, *H*-4 minor conformer, *H*-4 major conformer), 2.05−2.24 (m, 1,6H, *H*-3 both conformers, *H*CHCH=CH_2 major conformer), 2.24−2.40 (m, 1.4H, *H*-3 both conformers, *H*CHCH=CH_2 minor conformer), 2.57 (m, 0.4H, *H*CHCH=CH_2 minor conformer), 2.89 (m, 0.6H, *H*CHCH=CH_2 major conformer), 3.85 (s, 1.8H, COOC*H*$_3$ major conformer), 3.9 (s, 1.2H, COOC*H*$_3$ minor conformer), 4.39 (m, 0.6H, *H*-5 major conformer), 4.49 (m, 0.4H, *H*-5 minor conformer), 4.73 (m, 1H, *H*-2 both conformers), 5.04−5.2 (m, 2H, CH_2CH=C*H*$_2$ both conformers), 5.7−5.87 (m, 1H, CH_2C*H*=CH_2 both conformers); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 170.8, 170.3, 161.8, 157.9, 134.6, 134.3, 133.8, 118.1, 117.7, 117.4, 82.0, 81.6, 61.6, 60.7, 59.3, 59.1, 59.0, 52.6, 39.2, 39.0, 36.5, 36.2, 29.5, 29.2, 29.0, 27.8, 26.6; MS (FAB$^+$) *m/z* 298 [M + H]$^+$. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.74; H, 7.77; N, 4.64.

(2*R*,5*S*)-5-But-3-enyl-1-methoxyoxalylpyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 10. Compound **10** was prepared following the general procedure A. The crude was purified by flash chromatography (hexane/EtOAc 8:2) affording the pure product (79% over two steps) as colorless oil: $[\alpha]^{22}_D$ = −35.8 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) (1:2 mixture of conformers) δ 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.55−2.32 (m, 8H, C*H*$_2$-3, C*H*$_2$-4, C*H*$_2$$CH_2$CH=$CH_2$), 3.8 (s, 0.9H, COOC*H*$_3$ minor comformer), 3.84 (s, 2.1H, COOC*H*$_3$ major conformer), 4.21 (m, 1H, *H*-5), 4.36 (m, 0.3H, *H*-2 minor conformer), 4.67 (m, 0.7H, *H*-2 major conformer), 4.9−5.1 (m, 2H, CH_2CH_2CH=C*H*$_2$), 5.7−5.93 (m, 1H, CH_2CH_2C*H*=CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 170.9, 170.3, 162.2, 161.9, 158.4, 157.9, 137.7, 137.2, 115.2, 114.7, 82.0, 81.6, 61.3, 60.5, 59.5, 59.0, 57.4, 52.6, 34.0, 31.5, 30.5, 29.7, 29.3, 28.3, 27.8, 26.8; MS (FAB$^+$) *m/z* 312 [M + H]$^+$. Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.60; H, 8.19; N, 4.40.

(2*R*,5*R*)-5-Allyl-1-methoxyoxalylpyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 13. Compound **13** was prepared following the general procedure A. The crude was purified by flash chromatography (hexane/EtOAc 75:25) affording the pure product (76% over two steps) as colorless oil: $[\alpha]^{22}_D$ = −104.2 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) (1:3 mixture of conformers) δ 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.72−2.42 (m, 5H, C*H*$_2$-3, C*H*$_2$-4, *H*CHCH=CH_2), 2.48−2.64 (m, 1H, *H*CHCH=CH_2) 3.78 (s, 2.25H, COOC*H*$_3$ major conformer), 3.83 (s, 0.75H, COOC*H*$_3$, minor conformer), 4.28−4.72 (m, 1.25H, *H*-5 both conformers, *H*-2 minor conformer), 4.82 (m, 0.75H, *H*-2 major conformer), 4.98−5.2 (m, 2H, CH_2CH=C*H*$_2$), 5.55−5.84 (m, 1H, CH_2C*H*=CH_2); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 171.3, 170.1, 162.3, 158.4, 134.6, 133.9, 118.6, 117.9, 82.4, 81.9, 61.8, 60.7, 59.2, 58.7, 52.9, 40.3, 36.8, 29.4, 28.5, 28.0, 27.9, 26.5, 26.0; MS (FAB$^+$) *m/z* 298 [M + H]$^+$. Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.39; H, 7.94; N, 4.63.

(2*R*,5*R*)-5-But-3-enyl-1-methoxyoxalylpyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 16. Compound **16** was prepared following the general procedure A. The crude was purified by flash chromatography (hexane/EtOAc 65:35) affording the pure product (80% over two steps) as a colorless oil: $[\alpha]^{22}_D = -105.7$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (1:2 mixture of conformers) δ 1.35−1.45 (m, 2H, CH_2-$CH_2CH{=}CH_2$), 1.45 (s, 6.3H, C(CH_3)$_3$ major conformer), 1.47 (s, 2.7H, C(CH_3)$_3$ minor conformer), 1.64−1.77 (m, 1H, *H*-4), 1.8−1.92 (m, 1H, *H*-4), 1.93−2.29 (m, 3.3H, CH_2-3, CH_2*H*CH-CH=CH_2), 3.31−2.42 (m, 0.7H, *H*-3 major conformer), 3.6 (s, 2.1H. COOCH_3 major conformer), 3.75 (s, 0.9H, COOCH_3 minor conformer), 4.3−4.4 (m, 1H, *H*-5 both conformers), 4.42 (d, 0.3H, J = 9.12 Hz, *H*-2 minor conformer), 4.86 (d, 0.7H, J = 9.08 Hz, *H*-2 major conformer), 4.95−5.1 (m, 2H, CH_2CH_2-CH=CH_2), 5.72−5.80 (m, 1H, $CH_2CH_2CH{=}CH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 171.3, 170.2, 162.1, 158.3, 137.8, 137.2, 115.6, 115.0, 82.4, 81.9, 61.5, 60.3, 59.5, 58.7, 52.8, 52.6, 34.9, 31.6, 30.8, 29.5, 28.4, 28.0, 27.9, 26.7, 26.4; MS (FAB$^+$) m/z 312 [M + H]$^+$. Anal. Calcd for $C_{16}H_{25}NO_5$: C, 61.72; H, 8.09; N, 4.50. Found: C, 61.89; H, 7.99; N, 4.65.

General Procedure B. Reduction of the Methyl Ester. To a stirred solution of **7**, **10**, **13**, or **16** (0.23 mmol) in dry THF (2.3 mL), under argon and at −20 °C, was added 2 M $LiBH_4$ in THF (0.138 mL, 0.276 mmol). After 1 h, the temperature was raised at −10 °C and a saturated solution of NH_4Cl (2.3 mL) was added. The resulting mixture was extracted with EtOAc (3 × 2.5 mL), the combined organic phases were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography to give alcohols **8**, **11**, **14**, or **17**.

(2*R*,5*S*)-5-Allyl-1-(2-hydroxyacetyl)pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 8. Compound **8** was prepared following the general procedure B. The crude was purified by flash chromatography (hexane/EtOAc 7:3) affording the pure product (75%) as a colorless oil: $[\alpha]^{22}_D = -48.7$ (c = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of conformers) δ 1.45 (s, 9H, C(CH_3)$_3$), 1.63−2.5, (m, 4.5H, CH_2-3, CH_2-4, CH_2-CH=CH_2), 2.92 (m, 0.5H, *H*CHCH=CH_2 one conformer), 3.44 (m, 1H, O*H*), 3.7−4.44 (m, 4H, *H*-2, *H*-5, CH_2OH), 5.0−5.12 (m, 2H, $CH_2CH{=}CH_2$), 5.63−5.7 (m, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 171.3, 171.1, 170.8, 170.6, 134.8, 134.1, 118.6, 117.5, 82.9, 82.5, 60.8, 60.6, 60.6, 59.6, 59.1, 57.5, 38.8, 38.0, 29.9, 29.7, 28.3, 28.1, 28.0, 26.8; MS (FAB$^+$) m/z 270 [M + H]$^+$. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.25; H, 8.77; N, 5.26.

(2*R*,5*S*)-5-But-3-enyl-1-(2-hydroxyacetyl)pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 11. Compound **11** was prepared following the general procedure B. The crude was purified by flash chromatography (hexane/EtOAc 7:3) to the pure product (76%) as colorless oil: $[\alpha]^{22}_D = -43.1$ (c = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) (mixture of conformers) δ 1.46 (s, 9H, C(CH_3)$_3$), 1.6−2.35 (m, 8H, CH_2-3, CH_2-4, CH_2CH_2-CH=CH_2), 3.45 (bs, 1H, O*H*), 3.6−4.4 (m, 4H, *H*-2, *H*-5, CH_2-OH), 4.84−5.12 (m, 2H, $CH_2CH_2CH{=}CH_2$), 5.65−5.93 (m, 1H, $CH_2CH_2CH{=}CH_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 171.3, 171.0, 170.8, 170.5, 138.1, 137.0, 116.0, 114.9, 82.7, 81.6, 60.6, 60.5, 60.4, 59.4, 59.3, 57.2, 33.4, 32.9, 30.8, 30.7, 29.9, 29.8, 29.7, 28.9, 28.1, 28.0, 26.9; MS (FAB$^+$) m/z 284 [M + H]$^+$. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.75; H, 8.92; N, 4.80.

(2*R*,5*R*)-5-Allyl-1-(2-hydroxyacetyl)pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 14. Compound **14** was prepared following the general procedure B. The crude was purified by flash chromatography (hexane/EtOAc 6:4) affording the pure product (84%) as colorless oil: $[\alpha]^{22}_D = -85.7$ (c = 1.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mixture of conformers) δ 1.46 (s, 9H, C(CH_3)$_3$), 1.75−1.8 (m, 1H, *H*-4); 1.8−2.01 (m, 1H, *H*-4), 2.01−2.4 (m, 3.5H, CH_2-3, CH_2CH=CH_2) 2.70 (m, 0.5H, *H*CHCH=CH_2 one conformer), 3.81−3.9 (m, 1H, *H*-5 one conformer, *H*CHOH one conformer), 4.03 (d, 0.5H J = 15 Hz, *H*CHOH), 4.12 (d, 0.5H, J = 8.77 Hz, *H*-2 one conformer), 4.23 (s, 1H, CH_2OH one conformer), 4.35 (m, 0.5H, *H*-5 one conformer), 4.43 (d, 0.5H, J = 8.71 Hz, *H*-2 one conformer), 5.02−5.17 (m, 2H, $CH_2CH{=}CH_2$), 5.65−5.81 (m, 1H, $CH_2{-}CH{=}CH_2$); ^{13}C NMR (75.4 MHz, $CDCl_3$) (mixture of conformers) δ 170.8, 170.7, 170.5, 134.5, 133.3, 118.5, 117.6, 82.5, 81.3, 60.5, 60.3, 59.1, 58.3, 56.6, 39.1, 36.8, 29.5, 29.1, 28.1, 27.8, 27.2, 26.3, 25.8; MS (FAB$^+$) m/z 270 [M + H]$^+$. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.60; H, 8.55; N, 5.01.

(2*R*,5*R*)-5-But-3-enyl-1-(2-hydroxyacetyl)pyrrolidine-2-carboxylic Acid *tert*-Butyl Ester 17. Compound **17** was prepared following the general procedure B. The crude was purified by flash chromatography (hexane/EtOAc 6:4) affording the pure product (90%) as colorless oil: $[\alpha]^{22}_D = -84.9$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) (1:1 mixture of conformers) 1.25−1.42 (m, 1H, C$H_2CH_2CH{=}CH_2$ conformer A), 1.49 (s, 9H, C(CH_3)$_3$ both conformers), 1.53−1.7 (m, 1H, CH_2-$CH_2CH{=}CH_2$ conformer B), 1.78 (m, 0.5H, *H*-4 conformer A), 1.83 (m, 0.5H, *H*-4 conformer B), 1.93−2.2 (m, 4.5H, *H*-4, CH_2-3, $CH_2CH_2CH{=}CH_2$ both conformers), 2.31 (m, 0.5H, *H*-3 conformer A), 3.4 (m, 0.5H, O*H* one conformer), 3.44 (m, 0.5H, O*H* one conformer), 3.78−3.81 (m, 1H, *H*-5 conformer B, *H*CHOH one conformer), 4.02 (m, 0.5H, *H*CHOH one conformer), 4.11 (d, 0.5H, J = 8.4 H, *H*-2 conformer A), 4.28 (m, 0.5H, *H*-5 conformer A), 4.42 (m, 0.5H, J = 8.66 H, *H*-2 conformer B), 4.96−5.12 (m, 2H, $CH_2CH_2CH{=}CH_2$ both conformers), 5.75−5.9 (m, 1H, $CH_2CH_2CH{=}CH_2$ both conformers); ^{13}C NMR (50.3 MHz, $CDCl_3$) (mixture of conformers) δ 171.0, 170.9, 170.7, 137.8, 136.7, 116.1, 115.0, 82.7, 81.5, 60.7, 60.6, 60.2, 59.1, 58.9, 56.6, 34.0, 31.7, 30.9, 30.8, 29.4, 28.3, 28.0, 27.9, 26.6, 26.3; MS (FAB$^+$) m/z 284 [M + H]$^+$. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.70; H, 8.75; N, 5.00.

General Procedure C. Oxidation and 1,3-Dipolar Cycloaddition. To a stirred solution of oxalyl chloride (90 μL, 1.03 mmol) in dry CH_2Cl_2 (1.7 mL), under nitrogen and at −60 °C, was added dropwise DMSO (96 μL, 1.352 mmol). After 15 min, a solution of alcohol **8**, **11**, or **14** (0.338 mmol) in dry CH_2Cl_2 (1.7 mL) was added, and finally, after 25 min, TEA (376 μL, 2.7 mmol) was added. The reaction mixture was allowed to warm to 0 °C over 1 h, and then pH 7 phosphate buffer (3.4 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 3.5 mL), the combined organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was used for the next reaction without further purification.

To a solution of aldehyde **9**, **12**, or **15** (0.338 mmol) in EtOH/H_2O 9:1 (3.4 mL) were added *N*-benzylhydroxylamine hydrochloride (162 mg, 1.015 mmol) and $NaHCO_3$ (128 mg, 1.52 mmol), and the resulting mixture was refluxed for 6 h. After reaction completion, the solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with a saturated solution of NH_4Cl. The organic phase was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. To remove the excess *N*-benzylhydroxylamine, the crude was dissolved in CH_2Cl_2 and Amberlyst A21 was added until pH = 8, then at −20 °C, *tert*-butylacetyl chloride (282 μL, 2.03 mmol) was added. The reaction was stirred at room temperature for 15 min, and then the mixture was filtered and washed with CH_2Cl_2. Finally, the solvent was evaporated under reduce pressure and the crude was purified by flash chromatography to give the desired products **19**, **20**, and **21**.

General Procedure D. Oxidation and 1,3-Dipolar Cycloaddition. To a stirred solution of oxalyl chloride (216 μL, 2.457 mmol) in dry CH_2Cl_2 (5 mL), under nitrogen and at −60 °C, was added dropwise DMSO (240 μL, 3.35 mmol). After 15 min, a solution of alcohol **17** (0.780 mmol) in dry CH_2Cl_2 (5 mL) was added, and finally, after 25 min, TEA (913 μL, 6.55 mmol) was added. The reaction mixture was allowed to warm

to 0 °C over 1 h, and then pH 7 phosphate buffer (10 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude was used for the next reaction without further purification.

To a solution of aldehyde **18** (0.780 mmol) and *N*-benzylhydroxylamine hydrochloride (374 mg, 2.34 mmol) in toluene (20 mL) was added a solution of $NaHCO_3$ (330 mg, 3.90 mmol) in H_2O (10 mL), and the resulting mixture was refluxed for 20 h. After reaction completion, the solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and washed with a saturated solution of NH_4Cl. The organic phase was dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. To remove the excess of *N*-benzylhydroxylamine, the crude was dissolved in CH_2Cl_2 and Amberlyst A21 was added until pH = 8, then at −20 °C, *tert*-butylacetyl chloride (680 μL, 4.68 mmol) was added. The reaction was stirred at room temperature for 15 min, and then the mixture was filtered and washed with CH_2Cl_2. Finally, the solvent was evaporated under reduce pressure, and the crude was purified by flash chromatography to give the desired product **22a**.

(3a*S*,4a*R*,7*R*,8a*S*)-1-Benzyl-8-oxo-octahydro-2-oxa-1,7a-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butyl Ester 19. Compound **19** was prepared following procedure C. The crude was purified by flash chromatography (hexane/EtOAc 65:35) affording the pure product (74% over two steps) as colorless oil: $[\alpha]^{22}_D = -123.1$ (c = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, C(C*H*$_3$)$_3$), 1.62 (m, 1H, *H*-4), 1.88 (m, 1H, *H*-5), 2.0−2.2 (m, 4H, C*H*$_2$-6, *H*-4, *H*-5), 2.95 (m, 1H, *H*-3a), 3.22 (d, 1H, J = 9.0 Hz, *H*-8a), 3.58 (dd, 1H, J = 8.0 Hz, J = 6.1 Hz, *H*-3), 3.66 (m, 1H, *H*-4a), 3.92 (d, 1H, J = 14.3 Hz, CH*H*Ph), 4.17 (dd, 1H, J = 8.0 Hz, J = 8.0 Hz, *H*-3), 4.34 (dd, 1H, J = 8.6 Hz, J < 1 Hz, *H*-7), 4.90 (d, 1H, J = 14.3 Hz, C*H*HPh), 7.21−7.35 (m, 3H, aromatic protons), 7.4−7.46 (m, 2H, aromatic protons); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.8, 166.3, 137.8, 129.3, 128.0, 126.9, 81.5, 64.1, 62.0, 59.7, 59.1, 42.6, 33.0, 31.2, 29.7, 28.5, 27.9; MS (FAB$^+$) *m/z* 373 [M + H]$^+$. Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.89; H, 7.56; N, 7.44.

(3a*S*,5*R*,7a*S*,9a*S*)-1-Benzyl-4-oxodecahydro-2-oxa-3,4a-diazacyclopenta[*f*]azulene-5-carboxylic Acid *tert*-Butyl Ester 20. Compound **20** was prepared following the general procedure C. The crude was purified by flash chromatography (hexane/EtOAc 7:3) affording the pure product (75% over two steps) as a white solid: mp = 140−142 °C; $[\alpha]^{22}_D = -146.0$ (c = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, C(C*H*$_3$)$_3$), 1.63−1.94 (m, 4H, C*H*$_2$-9, *H*-7, *H*-8), 1.98−2.12 (m, 3H, C*H*$_2$-6, *H*-8), 2.27 (m, 1H, *H*-7), 2.79 (m, 1H, *H*-9a), 3.17 (d, 1H, J = 10.1 Hz, H-3a), 3.52 (dd, 1H, J = 7.6 Hz, J = 6.6 Hz, *H*-1), 3.67 (d, 1H, J = 13.6 Hz, CH*H*Ph), 3.85 (m, 1H, *H*-7a), 4.14 (dd, 1H, J = 8.5 Hz, J = 7.6 Hz, H-1), 4.47 (d, 1H, J = 13.6 Hz, C*H*HPh), 4.65 (dd, 1H, J = 7.4 Hz, J = 3.6 Hz, *H*-5), 7.21−7.35 (m, 3H, aromatic protons), 7.41−7.44 (m, 2H, aromatic protons); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.2, 168.5, 137.3, 129.3, 128.1, 127.1, 81.4, 73.2, 71.4, 61.4, 60.7, 58.8, 44.9, 34.0, 33.2, 32.2, 29.7, 28.0, 27.6; MS (FAB$^+$) *m/z* 387 [M + H]$^+$. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.45; H, 7.84; N, 7.06.

(3a*R*,4a*S*,7*R*,8a*R*)-1-Benzyl-8-oxooctahydro-2-oxa-1,7a-diaza-*s*-indacene-7-carboxylic Acid *tert*-Butyl Ester 21. Compound **21** was prepared following the general procedure C. The crude was purified by flash chromatography (hexane/EtOAc 7:3) affording the pure product (85% over two steps) as a white solid: mp = 175 °C; $[\alpha]^{22}_D = +9.4$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H, C(C*H*$_3$)$_3$), 1.50−1.65 (m, 2H, *H*-4, *H*-5), 1.83 (m, 1H, *H*-6), 2.12 (m, 1H, *H*-4), 2.20 (m, 1H, *H*-5), 2.40 (m, 1H, *H*-6), 2.98 (m, 1H, *H*-3a), 3.36 (d, 1H, J = 8 Hz, *H*-8a), 3.62 (m, 1H, *H*-3), 3.78 (m, 1H, *H*-4a), 3.93 (d, 1H, J = 14.3, HC*H*Ph), 4.15 (dd, 1H, J1 = J2 = 7.7 Hz, *H*-3), 4.48 (dd, 1H, J1 = J2 = 8.64 Hz, *H*-7), 4.82 (d, 1H, J = 14.3, NC*H*$_2$Ph), 7.23−7.34 (m, 3H, aromatic protons), 7.43−7.45 (m, 2H, aromatic protons); ^{13}C NMR (HETCOR, 400 MHz, $CDCl_3$) δ 129.7, 128.4, 127.3, 71.3, 65.0, 63.0, 59.3, 59.1, 42.4, 32.8, 32.9, 33.0, 28.5, 28.4; MS (FAB$^+$) *m/z* 373 [M + H]$^+$. Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.87; H, 7.66; N, 7.28.

(3a*R*,5*R*,7a*R*,9a*R*)-1-Benzyl-4-oxodecahydro-2-oxa-3,4a-diazacyclopenta[*f*]azulene-5-carboxylic Acid *tert*-Butyl Ester 22a. Compound **22a** was prepared following the general procedure D. The crude was purified by flash chromatography (hexane/EtOAc 4:6) affording pure **22a** (55% over two steps) as a white solid: mp = 123 °C; $[\alpha]^{22}_D = +70.6$ (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H, C(C*H*$_3$)$_3$), 1.54 (m, 1H, *H*-8), 1.65−1.75 (m, 3H, *H*-9, *H*-8, *H*-7), 1.95 (m, 1H, *H*-6), 2.06 (m, 1H, *H*-9), 2.17 (m, 1H, *H*-6), 2.35 (m, 1H, *H*-7), 2.63 (m, 1H, *H*-9a), 3.26 (d, 1H, J = 10.19 Hz, *H*-3a), 3.47 (dd, 1H, J1 = J2 = 6.4 Hz, *H*-1), 3.69 (d, 1H, J = 13.88, HC*H*Ph), 4.00 (m, 1H, H-7a), 4.10 (dd, 1H, J1 = J2 = 6.4 Hz, *H*-1), 4.50 (d, 1H, J = 13.88, HC*H*Ph), 4.54 (dd, 1H, J = 10,23 Hz, J = 2.34 Hz, *H*-5), 7.22−7.41 (m, 3H, aromatic protons), 7.42−7.5 (m, 2H, aromatic protons); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.3, 168.9, 137.4, 129.5, 129.4, 128.3, 127.3, 81.5, 73.0, 71.6, 61.2, 58.6, 45.1, 34.8, 32.7, 32.2, 29.8, 28.1, 27.2; MS (FAB$^+$) *m/z* 387 [M + H]$^+$. Anal. Calcd for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.45; H, 7.99; N, 7.06.

General Procedure E. Hydrogenolysis. A solution of **19**, **20**, **21**, or **22** (0.10 mmol) in MeOH (1.0 mL) containing a catalytic amount of 10% Pd−C was stirred under hydrogen for ca. 2 h. After reaction completion, the mixture was filtered through a Celite pad and washed with MeOH. The collected organic phase was evaporated under reduced pressure affording the corresponding amino alcohols **23**−**26**.

(3*S*,4*S*,6*R*,9*S*)-3-Amino-1-aza-2-oxo-4-hydroxymethylbicyclo[4.3.0]nonanecarboxylic Acid *tert*-Butyl Ester 23. Compound **23** was prepared following the general procedure E. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 9:1, EtOAc/MeOH 9:1) affording the pure product (99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1H, *H*-5), 1.48 (s, 9H, C(C*H*$_3$)$_3$), 1.7 (m, 1H, *H*-7), 1.9−2.25 (m, 4H, *H*-5, *H*-7, C*H*$_2$-8), 2.39 (m, 1H, *H*-4), 3.6 (m, 1H, *H*-6), 3.67 (m, H, H-3), 3.72−3.78 (m, 2H, C*H*$_2$OH), 4.38 (m, 1H, *H*-9); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.0, 169.9, 82.0, 65.5, 59.3, 56.9, 53.3, 38.0, 32.0, 30.7, 29.8, 29.1, 28.1; MS (FAB$^+$) *m/z* 285 [M + H]$^+$. Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.20; H, 8.52; N 9.85. Found: C, 59.13; H, 8.51; N, 9.85.

(3*S*,4*S*,7*S*,10*S*)-3-Benzyalmino-1-aza-2-oxo-4-hydroxymethylbicyclo[5.3.0]decanecarboxylic Acid *tert*-Butyl Ester 24. Compound **24** was prepared following the general procedure E. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 9:1, EtOAc/MeOH 9:1) affording the pure product (90%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38−1.4 (m, 1H, *H-5*), 1.46 (s, 9H, C(C*H*$_3$)$_3$), 1.60−1.93 (m, 5H, *H*-4, *H*-5, C*H*$_2$-6, *H*-8), 1.93−2.17 (m, 2H, C*H*$_2$-9), 2.23 (m, 1H, *H*-8), 3.50 (d, 1H, J = 9.5 Hz, *H*-3), 3.66 (d, 2H, J = 5.5 Hz, C*H*$_2$OH), 3.75 (m, 1H, *H*-7), 4.54 (dd, 1H, J = 6 Hz, J = 5.4 Hz, *H*-10); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.0, 171.1, 81.4, 68.0, 61.6, 58.3, 58.0, 40.8, 33.5, 32.9, 32.7, 32.0, 29.6, 27.9, 27.7; MS (FAB$^+$) *m/z* 299 [M + H]$^+$. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.40; H, 8.77; N, 9.40. Found: C, 60.38; H, 8.77; N, 9.39.

(3*R*,4*R*,6*S*,9*S*)-3-Benzylamino-1-aza-2-oxo-4-hydroxymethylbicyclo[4.3.0]nonanecarboxylic Acid *tert*-Butyl Ester 25. Compound **25** was prepared following the general procedure E. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 9:1, EtOAc/MeOH 9:1) affording the pure product (98%) as a colorless oil: $[\alpha]^{22}_D = -79$ (c = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.3 (m, 1H, *H*-5), 1.48 (s, 9H, C(C*H*$_3$)$_3$), 1.53 (m, 1H, *H*-7), 1.85 (m, 1H, *H*-8), 2.06 (m, 1H, *H*-5), 2.21 (m, 1H, *H*-7), 2.26−2.38 (m, 2H, *H*-8, *H*-4), 3.62−3.8 (m, 4 H, C*H*$_2$OH, *H*-3, *H*-6), 4.43 (m, 1 H, *H*-9); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.2, 170.7, 81.7, 65.3, 59.0, 57.5, 52.9, 38.4, 32.7, 29.4, 28.0, 27.9; MS (FAB$^+$) *m/z* 285 [M + H]$^+$. Anal.

Calcd for $C_{14}H_{24}N_2O_4$: C, 59.15; H, 8.52; N, 9.85. Found: C, 59.13; H, 8.51; N, 9.85.

(3*R*,4*R*,7*R*,10*S*)-3-Benzylamino-1-aza-2-oxo-4-hydroxymethylbicyclo[5.3.0]decanecarboxylic Acid *tert*-Butyl Ester 26. Compound **26** was prepared following the general procedure E. The crude was purified by flash chromatography (CH_2Cl_2/MeOH 9:1, EtOAc/MeOH 9:1) affording the pure product (90%) as colorless oil: $[\alpha]^{22}_D = -6.22$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H, C(C*H*$_3$)$_3$), 1.48−1.57 (m, 2H, *H*-5, *H*-6), 1.57−1.82 (m, 4H, *H*-4, *H*-5, *H*-6, *H*-8), 1.95 (m, 1H, *H*-9), 2.2 (m, 1H, *H*-9), 3.32 (m, 1H, *H*-8), 3.54 (m, 1H, *H*CHOH), 3.6−3.76 (m, 2H, *H*CHOH, *H*-3), 3.95 (m, 1H, *H*-7), 4.53 (m, 1H, *H*-10); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.6, 168.1, 82.2, 64.5, 61.7, 58.3, 56.4, 38.1, 32.3, 32.1, 29.9, 28.1, 27.2; MS (FAB$^+$) *m/z* 299 [M + H]$^+$. Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.40; H, 8.78; N, 9.40. Found: C, 60.38; H, 8.77; N, 9.39.

General Procedure F. Selective Cleavage of N−O Bound. To compound **19**, **20**, **21**, or **22** (0.052 mmol), under argon and at room temperature, was added a commercial solution of 0.1 M SmI_2 in THF until the resulting solution was permanently blue (5.2 mL, 0.52 mmol). The reaction mixture was stirred for ca. 30 min, and then a 0.5 M solution of NH_3 in EtOH (6 mL) was added and the mixture was stirred for 20 min. Finally H_2O was added, and the mixture was saturated with Na_2SO_4. The aqueous phase was extracted with diisopropyl ether (3 × 10 mL), and the organic phase, dried with Na_2SO_4, was evaporated under reduced pressure. The crude was purified by flash chromatography yielding **27**, **28**, **29**, or **30**.

(3*S*,4*S*,6*R*,9*S*)-3-Benzylamino-1-aza-2-oxo-4-hydroxymethylbicyclo[4.3.0]nonanecarboxylic Acid *tert*-Butyl Ester 27. Compound **27** was prepared following the general procedure F. The crude was purified by flash chromatography (EtOAc/Hexane 8:2) affording the pure product (70%) as an amorphous solid: $[\alpha]^{22}_D = -57.72$ ($c = 1.01$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (m, 1H, *H*-5), 1.48 (s, 9H, C(C*H*$_3$)$_3$),1.62 (m, 1H, *H*-7), 2.0−2.26 (m, 4H, *H*-5, *H*-7 C*H*$_2$-8), 2.53 (m, 1H, *H*-4), 3.33 (d, 1H, $J = 6.8$ Hz, *H*-3), 3.43−3.53 (m, 2H, *H*-6, *H*CHOH), 3.68 (dd, 1H, $J = 9.2$ Hz, $J = 11.6$ Hz, *H*CHOH), 3.81 (d, 1H, $J = 13.2$ Hz, *H*CHPh), 3.9 (d, 1H, $J = 13.2$ Hz, *H*CHPh), 4.3 (d, 1H, $J = 8.4$ Hz, *H*-9), 7.26 (m, 1H, aromatic proton), 7.3−7.38 (m, 4H, aromatic protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.84, 169.3, 138.9, 131.6, 128.6, 128.4, 127.3, 81.8, 66.9, 59.9, 59.0, 55.9, 52.7, 36.5, 32.1, 31.1, 29.7, 29.1, 28.0; MS (FAB$^+$) *m/z* 375 [M + H]$^+$. Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07; N, 7.48. Found: C, 67.4; H, 8.04; N, 7.51.

(3*S*,4*S*,7*S*,10*S*)-3-Benzyalmino-1-aza-2-oxo-4-hydroxymethylbicyclo[5.3.0]decanecarboxylic Acid *tert*-Butyl Ester 28. Compound **28** was prepared following the general procedure F. The crude was purified by flash chromatography (EtOAc/Hexane 8:2) affording the pure product (80%) as an amorphous solid: $[\alpha]^{22}_D = -80.5$ ($c = 1.50$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (m, 1H, *H*-5), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.62−1.8 (m, 5H, *H*-4, *H*-5, C*H*$_2$-6, *H*-8), 1.81−2.1 (m, 2H, C*H*$_2$-9), 2.17 (m, 1H, *H*-8), 3.16 (d, 1H, $J = 10$ Hz, *H*-3), 3.43−3.48 (m, 3H, *H*CHPh, C*H*$_2$OH), 3.7 (m, 1H, *H*-7), 3.8 (d, 1H, $J = 12.4$ Hz, *H*CHPh), 4.46 (dd, 1H, $J = 4$ Hz, $J = 8.4$ Hz, *H*-10), 7.16−7.3 (m, 5H, aromatic proton); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.6, 171.1, 139.2, 128.6, 128.5, 127.3, 81.5, 68.2, 65.1, 61.5, 58.3, 54.4, 40.6, 33.3, 33.0, 31.7, 29.7, 28.0, 27.8; MS (FAB$^+$) *m/z* 389 [M + H]$^+$. Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.0; H, 8.32; N, 7.23.

(3*R*,4*R*,6*S*,9*S*)-3-Benzylamino-1-aza-2-oxo-4-hydroxymethylbicyclo[4.3.0]nonanecarboxylic Acid *tert*-Butyl Ester 29. Compound **29** was prepared following the general procedure F. The crude was purified by flash chromatography (EtOAc/Hexane 8:2) affording the pure product (68%) as an amorphous solid: $[\alpha]^{22}_D = -51.8$ ($c = 1.11$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (m, 1H, *H*-5), 1.48 (s, 9H, C(C*H*$_3$)$_3$),1.55 (m, 1H, *H*-7), 1.88 (m, 1H, *H*-8), 2.15 (m, 1H, *H*-5), 2.23 (m, 1H, *H*-7), 2.29 (m, 1H, *H*-8), 2.46 (m, 1H, *H*-4), 3.52 (d, 1H, $J = 6.3$ Hz, *H*-3), 3.57−3.66 (m, 2H, C*H*$_2$OH), 3.72 (m, 1H, $J =$, *H*-6), 3.94 (d, 1H, $J = 12.8$ Hz, *H*CHPh), 3.4 (d, 1H, $J = 12.8$ Hz, *H*CHPh), 4.48 (dd, 1H, $J = 7.2$ Hz, $J = 7.8$ Hz, *H*-9), 7.28 (m, 1H, aromatic proton), 7.3−7.38 (m, 4H, aromatic protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 171.1, 169.1, 138.9, 128.6, 128.4, 127.4, 81.7, 66.4, 59.9, 59.0, 55.8, 53.1, 36.0, 32.6, 30.4, 28.0, 27.9; MS (FAB$^+$) *m/z* 375 [M + H]$^+$. Anal. Calcd for $C_{21}H_{30}N_2O_4$: C, 67.35; H, 8.07; N, 7.48. Found: C, 67.32; H, 8.09; N, 7.50.

(3*R*,4*R*,7*R*,10*S*)-3-Benzylamino-1-aza-2-oxo-4-hydroxymethylbicyclo[5.3.0]decanecarboxylic Acid *tert*-Butyl Ester 30. Compound **30** was prepared following the general procedure F. The crude was purified by flash chromatography (EtOAc/Hexane 8:2) affording the pure product (78%) as an amorphous solid: $[\alpha]^{22}_D = +23.96$ ($c = 1.01$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34−1.5 (m, 2H, *H*-5, *H*-6), 1.51 (s, 9H, C(C*H*$_3$)$_3$),1.6−1.77 (m, 4H, *H*-4, *H*-5, *H*-6, *H*-8), 1.96 (m, 1H, *H*-9), 2.2 (m, 1H, *H*-9), 2.31 (m, 1H, *H*-9), 3.31 (d, 1H, $J =$ 10.09 Hz, *H*-3), 3.5−3.59 (m, 3H, *H*CHPh, C*H*$_2$OH), 3.87 (d, 1H, $J = 12.31$ Hz, *H*CHPh), 3.93 (m, 1H, *H*-7), 4.55 (dd, 1H, $J = 8.5$ Hz, $J = 3.3$ Hz, *H*-10), 7.28 (m, 1H, aromatic proton), 7.3−7.4 (m, 4H, aromatic protons); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ171.9, 171.0, 139.2, 128.7, 128.5, 127.3, 81.4, 68.2, 65.2, 61.2, 57.9, 54.1, 40.7, 33.7, 32.5, 31.14, 29.7, 28.0, 27.3; MS (FAB$^+$) *m/z* 389 [M + H]$^+$. Anal. Calcd for $C_{22}H_{32}N_2O_4$: C, 68.01; H, 8.30; N, 7.21. Found: C, 68.03; H, 8.28; N, 7.22.

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Supporting Information Available: Compound characterization for all compounds and MO discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

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