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A novel stereoselective tin-free radical protocol for the enantioselective synthesis of pyrrolidinones and its application to the synthesis of biologically active GABA-derivatives

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Abstract

Optically pure 4-alkyl-pyrrolin-2-ones were synthesized from chiral *N*-allyl-α-bromoacetamides in high selective and stereo-controlled fashion, via a sequential 5-*exo-trig* radical cyclization-hydrogen or bromine atom-transfer process, under non-tin conditions. Interestingly, when *N*-allyl-α-bromoacetamides were treated with triethylborane/MeOH(excess)/$BF_3 \cdot OEt_2$ in toluene at −78 °C, a tandem 5-*exo-trig* radical cyclization-hydrogen atom-transfer reaction operated, on the other hand, a tandem 5-*exo-trig* radical cyclization-bromine atom-transfer reaction proceeded in good yield and high stereoselectivity when the reaction was carried out with equimolar amounts of MeOH in THF at −78 °C. Thus, optically pure 4-alkyl-pyrrolin-2-ones were synthesized via this tin-free radical pathway and transformed to their corresponding biologically active GABA-derivatives, Pregabalin and CAMP.

1. Introduction

Although free radical reactions have emerged as a powerful tool for the construction of heterocyclic compounds,[1] there still are issues related to the chemo, regio, and stereoselectivities of those reactions, not to mention that in most of the cases, the free radical methods usually involve the use of toxic reagents, such as reagents based on tin, cobalt, manganese, or samarium.[2] In spite of the introduction of non-tin radical reagents such as silyl[3] and thiyl reagents,[4] researchers continue to investigate new reaction systems to generate free radicals capable to carry out free radical reactions under non-toxic conditions with good chemo, regio, and stereoselectivities.

In this regard, Wood and co-workers turned the classical tin-mediated-Barton–McCombie deoxygenation protocol into a pretty environmental reaction.[5] Their novel protocol consisted the use of BEt_3 as radical initiator[6] and $BEt_3 \cdot H_2O$ complex as source of hydrogen atom. Apparently, such complex serves to weaken the O–H bond, so hydrogen atom-transfer process is highly favored. Deuterium labeling experiments and theoretical calculations suggested that this process operated as a free radical chain pathway. Based on those results, we thought that this protocol might work similarly with alkyl halides to generate their corresponding alkyl radicals, so then if we apply it to a recently reported stereoselective 5-*exo-trig* radical cyclization protocol of converting chiral allylic amides **1** to 4-alkyl-pyrrolidin-2-ones **2** for the enantioselective synthesis of GABA-derivatives,[7] we would have developed an environmentally friendly protocol for the enantioselective synthesis of GABA-derivatives (Scheme 1).[8]

2. Results

Toward this end, chiral allylic amides (*S*)-**3** and (*S*)-**4** were prepared according to literature procedure[7,9] and exposed under Wood's conditions at −78 °C[5] using $BF_3 \cdot OEt_2$ as Lewis acid.

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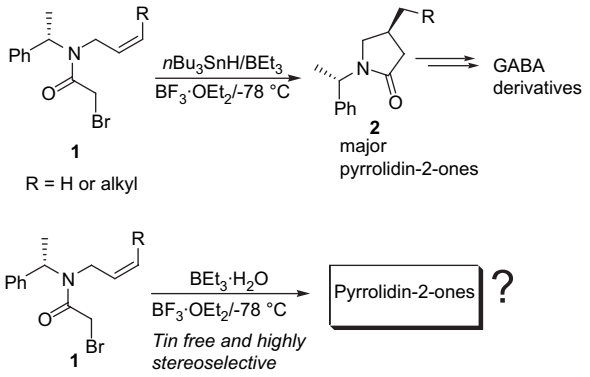
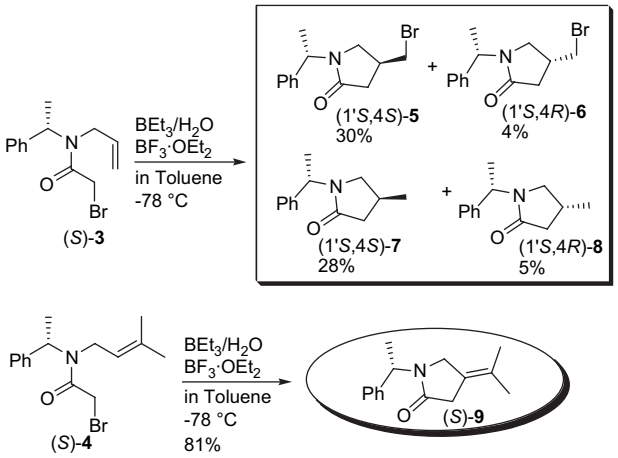


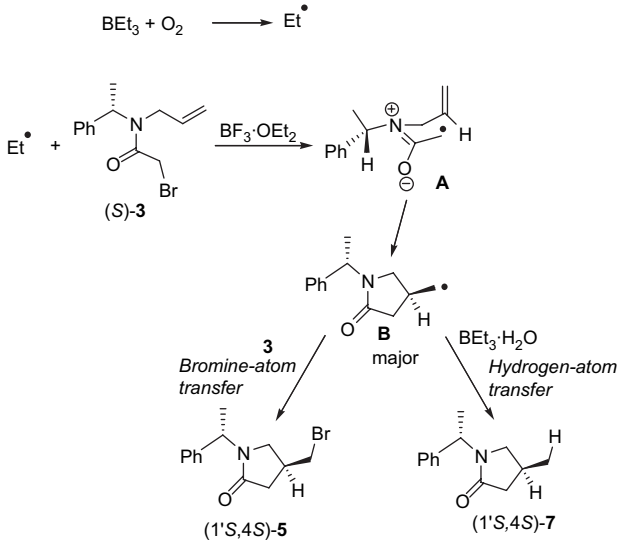
Scheme 1. Real and hypothetic 5-*exo-trig* radical cyclization.

As we can see from Scheme 2, amide (*S*)-**3** afforded two pairs of diastereomeric pyrrolidinones (1′*S*,4*S*)-**5** and (1′*S*,4*R*)-**6**, and (1′*S*,4*S*)-**7** and (1′*S*,4*R*)-**8**.[10] On the other hand amide (*S*)-**4** afforded only one pyrrolidinone (*S*)-**9**. Very interestingly, the first pair of pyrrolidinones (1′*S*,4*S*)-**5** and (1′*S*,4*R*)-**6** retained the bromine atom at terminal position, which suggests that an unusual bromine atom-transfer process (compared to iodine atom transfer[11]) occurred after the stereoselective 5-*exo-trig* radical cyclization process.[12] The same stereochemical outcome was observed for pyrrolidinones (1′*S*,4*S*)-**7** and (1′*S*,4*R*)-**8**, however, a hydrogen atom transfer occurred instead of the bromine atom transfer. It is important to note that the stereochemical outcome is in accordance with the stereochemical model previously reported, where the major pyrrolidinones correspond to those with *S* absolute stereochemistry at C4.[7]



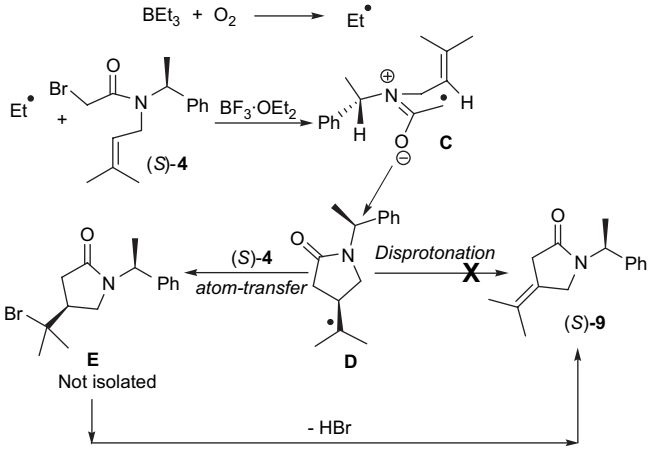
Scheme 2. 5-*exo-trig* Radical cyclization $BEt_3 \cdot H_2O$ complex-mediated in the presence of $BF_3 \cdot OEt_2$.

Based on Wood's proposal for the Barton deoxygenation in the presence of $BEt_3 \cdot H_2O$ complex, we also proposed a free radical process for the reaction of (*S*)-**3** which was initiated by BEt_3 and oxygen followed by the propagation step where BF_3OEt_2-mediated stereoselective 5-*exo-trig* cyclization (**A** to **B**) followed by bromine or hydrogen atom transfer (Scheme 3). On the other hand, amide (*S*)-**4** underwent non-chain radical pathway to give pyrrolidinone (*S*)-**9** as the single product (Scheme 4). We initially thought that perhaps pyrrolidinone



Scheme 3. Radical cyclization-bromine or hydrogen atom-transfer sequence.

(*S*)-**9** could be formed by a disproportionation reaction of tertiary radical **D**, due to its high stability and steric hindrance, however, due to the high chemical yield of (*S*)-**9** and the non-observation of reduction product of (*S*)-**4** (not shown), we believe that bromine atom process operates, which would result in possible formation of a tertiary and labile bromine **E** giving thus (*S*)-**9** in good yield[13] (**E** to (*S*)-**9**). See Scheme 4.

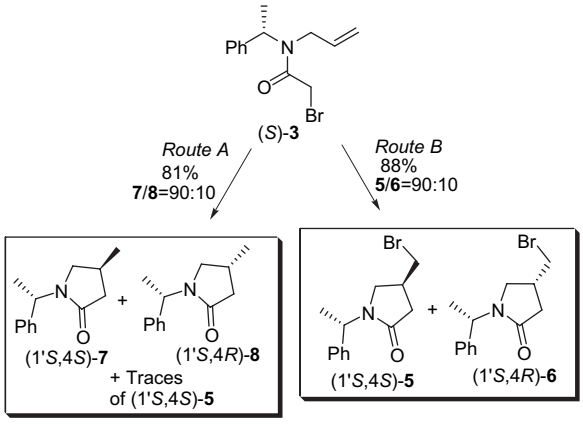


Scheme 4. Non-radical chain reaction of (*S*)-**4** to pyrrolidinone (*S*)-**9**.

This novel stereoselective tin-free radical cyclization coupled with the unusual bromine atom-transfer process prompted us to seek a more efficient and general method to improve the stereoselectivity and selective atom-transfer process.

Taking into account that water crystallizes below 0 °C (so this may be the reason of the poor incorporation of hydrogen atom) we decided to use methanol instead of water with the expectation that it may work similarly to water. As Wood established that water (or in our case methanol) was necessary for the free radical propagation step and the hydrogen atom transfer, we thought that by reducing the amounts of the source of the hydrogen atom, the bromine atom-transfer pathway should be

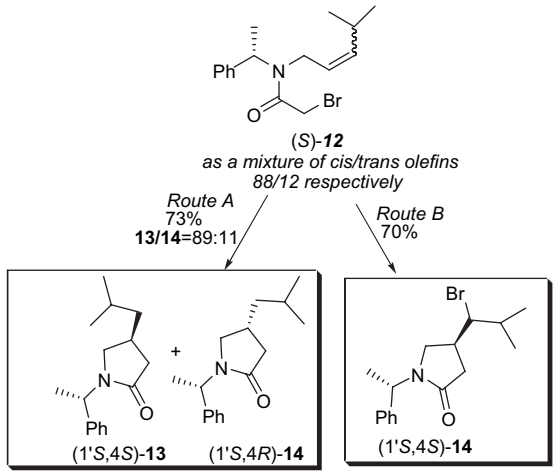
favored. Thus after many attempts (including different solvents, excess of BEt_3 and $BF_3{\cdot}OEt_2$, and longer reaction times), when amide (*S*)-**3** was treated with 5 equiv of BEt_3, 1.5 equiv of MeOH in well degassed and dried toluene in the presence of 3 equiv of $BF_3{\cdot}OEt_2$, pyrrolidinones (1′*S*,4*S*)-**5** and (1′*S*,4*R*)-**6** were obtained in good yield and good stereoselectivity (route B, Scheme 5). On the other hand, when amide (*S*)-**3** was treated with 5 equiv of BEt_3 and the 20 equiv of MeOH in well degassed and dried THF in the presence of 3 equiv of $BF_3{\cdot}OEt_2$, pyrrolidinones (1′*S*,4*S*)-**7** and (1′*S*,4*R*)-**8** were obtained in good yield and good stereoselectivity, and only trace amount of pyrrolidinone (1′*S*,4*S*)-**5** was observed (Scheme 5).



Scheme 5. Selective and stereoselective synthesis of pyrrolidinones via free tin 5-*exo*-*trig* radical cyclization. Conditions and reagents. *Route A*: 5 equiv of BEt_3/MeOH (20 equiv), 3 equiv of $BF_3{\cdot}OEt_2$ in THF at −78 °C. *Route B*: 5 equiv of BEt_3/MeOH (2 equiv), 3 equiv of $BF_3{\cdot}OEt_2$ in toluene at −78 °C.

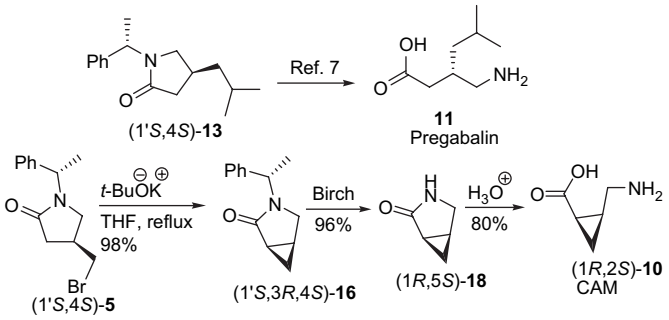
With this novel tin-free chemo and stereoselective radical protocol for the synthesis of optically pure pyrrolidinones in hand, we decided to apply it to the enantioselective synthesis of two pharmacologically important γ-amino acids: the (1*R*,2*S*)-2-(aminomethyl)cyclopropanecarboxylic acid (CAMP, **10**[14]) and (*S*)-3-aminomethyl-5-methylhexanoic acid (Pregabaline, **11**[15]). For the synthesis of Pregabalin **11**, allylic amide (*S*)-**12** was prepared according to literature procedure.[7] With this compound in hand, a mixture of cis/trans amide (*S*)-**12** was exposed to the improved hydrogen atom-transfer reaction conditions to afford the cyclization-hydrogen atom-transfer products pyrrolidinones (1′*S*,4*S*)-**13** and (1′*S*,4*R*)-**14** in 73% with a ratio of 93:7 (route A, Scheme 6). To further explore the generality of this novel protocol, the same amide (*S*)-**12** was exposed to the conditions for the generation of the cyclization-bromine atom-transfer product, and pyrrolidinone (1′*S*,4*S*)-**15**[16] was obtained as an inseparable mixture of C−Br epimers (route B, Scheme 6).

Finally, pyrrolidinone (1′*S*,4*S*)-**13** was converted to optically pure (*S*)-3-aminomethyl-5-methylhexanoic acid Pregabalin **11** in good yield (70%) and high optical purity (up to 98% ee) according to literature preocedure.[7] On the other hand, pyrrolidinone (1′*S*,4*S*)-**5** was first transformed to its corresponding cyclopropane derivative (1′*S*,1*R*,5*S*)-**16** followed by debenzylation affording (1*R*,5*S*)-**18**[14c] and finally by acid hydrolysis to give optically pure (1*R*,2*S*)-2-(aminomethyl)cyclopropanecarboxylic acid



Scheme 6. Synthesis of Pregabalin precursor **14**. Conditions and reagents. *Route A*: 5 equiv of BEt_3/MeOH (20 equiv), 3 equiv of $BF_3{\cdot}OEt_2$ in THF at −78 °C. *Route B*: 5 equiv of BEt_3/MeOH (2 equiv), 3 equiv of $BF_3{\cdot}OEt_2$ in toluene at −78 °C.

(CAMP, **10**) in good yield and high optical purity (up to 98% ee,[14c] Scheme 7).



Scheme 7. Synthesis of biologically active γ-amino acids.

It is worthy to mention that with this novel protocol of radical cyclization-bromine atom-transfer reaction, the synthesis of CAMP was reduced by five steps comparing to the synthetic route previously reported.[14c]

In conclusion, we have developed a novel stereoselective and tin-free protocol for the synthesis of 4-alkyl-pyrrolidin-2-ones from chiral *N*-allyl-α-bromoacetamides via a tandem 5-*exo*-*trig* radical cyclization-hydrogen or bromine atom-transfer reaction. The enormous potential of this reaction was showcased in the synthesis of two important γ-amino acids.

3. Experimental

3.1. General protocol for cyclization-hydrogen atom transfer

To a solution of (*S*)-2-bromo-*N*-(4-methyl-pent-2-enyl)-*N*-(1-phenyl-ethyl)-acetamide (*S*)-**12**[7] (0.5 g, 1.7 mmol) in THF (40 mL) at −78 °C were added triethylborane (1 g, 10.2 mmol of a 1 M solution in hexane) and $BF_3{\cdot}OEt$ (0.7 g, 5.1 mmol). The resulting solution was stirred for 15 min before adding methanol (2 mL, 40.8 mmol). Then, an air balloon was

placed to the flask of reaction and was stirred for 6 h to ensure completion. Finally, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography through silica gel (230–400 mesh) with hexane/EtOAc (v/v=5:1) giving 0.4 g of (1′*S*,4*S*)-**13**[7] as colorless oil in 73% yield, and traces of (1′*S*,4*R*)-**14**.

3.2. General protocol for cyclization-bromine atom transfer

To a solution of (*S*)-*N*-allyl-2-bromo-*N*-(1-phenyl-ethyl)-acetamide (*S*)-**3**[7,9] (0.27 g, 0.93 mmol) in dry toluene (50 mL) at −78 °C were added triethylborane (0.4 g, 2.81 mmol of a 1 M solution in hexane) and $BF_3 \cdot OEt$ (0.5 g, 5.63 mmol). The resulting solution was stirred for 15 min before adding methanol (0.8 mL, 2.81 mmol). Then, an air balloon was placed to the flask of reaction and was stirred for 6 h to ensure completion. Finally, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography through silica gel (230–400 mesh) with hexane/EtOAc (v/v=5:1) giving 0.23 g (86% yield) of (1′*S*,4*S*)-**5** as major diastereoisomer and 0.04 g (4%) of (1′*S*,4*R*)-**6** as the minor diastereoisomer, both as colorless oil.

3.2.1. (1′S,4S)-4-Bromomethyl-1-(1-phenyleth-1′-yl)-pyrrolidin-2-one (5)

The title compound was obtained in 86% yield as colorless oil. $[\alpha]_D$ −78.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.53 (d, 3H, *J*=6.8 Hz), 2.30 (dd, 1H, *J*=15.6, 6.0 Hz), 2.60 (dd, 1H, *J*=15.6, 8.8 Hz), 2.65 (m, 1H), 3.14 (br d, 2H, *J*=6.8 Hz), 3.37 (dd, 1H, *J*=10.4, 7.6 Hz), 3.43 (dd, 1H, *J*=10.4, 5.6 Hz), 5.49 (q, 1H, 7.2 Hz), 7.26–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 15.8, 33.2, 35.7, 36.7, 46.6, 48.8, 126.8, 127.4, 128.4, 139.6, 172.2. IR (CCl_4) *ν* 3433, 2931,1682, 1422, 1275 cm^{-1}. FAB-HRMS *m/z* calcd for $C_{13}H_{16}BrNO$ $[M+H]^+$: 282.0494. Found: 282.0491.

3.2.2. (1′S,4R)-4-Bromomethyl-1-(1-phenyleth-1′-yl)-pyrrolidin-2-one (6)

The title compound was obtained in 4% yield as colorless oil. $[\alpha]_D$ −112.4 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.44 (d, 3H, *J*=7.2 Hz), 2.18 (dd, 1H, *J*=16.4, 5.6 Hz), 2.55 (dd, 1H, *J*=16.4, 8.8 Hz), 2.64 (m, 1H), 2.70 (dd, 1H, *J*=9.6, 5.6 Hz), 3.12 (dd, 1H, *J*=10.0, 7.2 Hz), 3.22 (dd, 1H, *J*=10.0, 5.6 Hz), 3.40 (dd, 1H, *J*=9.6, 7.6 Hz), 5.41 (q, 1H, *J*=7.2 Hz), 7.23–7.25 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 15.9, 33.6, 35.4, 36.8, 46.6, 48.8, 126.8, 127.4, 128.4, 139.4, 172.2. IR (CCl_4) *ν* 3434, 2933, 1684, 1423, 1276 cm^{-1}. FAB-HRMS *m/z* calcd for $C_{13}H_{16}BrNO$ $[M+H]^+$: 282.0494. Found: 282.0492.

3.2.3. (1S)-4-Isopropylidene-1-(phenyleth-1′-yl)-pyrrolidin-2-one (9)

The title compound was obtained in 81% yield as colorless oil. $[\alpha]_D$ −48.9 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHZ, $CDCl_3$) *δ*: 1.52 (br s, 3H), 1.55 (d, 3H, *J*=7.2 Hz), 1.62 (apparent t, 3H, *J*=1.8 Hz), 3.07 (br s, 2H), 3.52 (d sept, 1H, *J*=13.5, 1.5 Hz), 3.89 (d sept, 1H, *J*=13.5, 1.5 Hz), 5.62 (q, 1H, *J*=7.2 Hz), 7.20–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 15.9, 19.5, 20.9, 36.2, 46.3, 48.6, 119.9, 125.8, 127.1, 127.4, 128.5, 139.9, 173.0. IR (CCl_4) *ν* 3342, 2977, 1702, 1664, 1495 cm^{-1}. FAB-HRMS *m/z* calcd for $C_{15}H_{20}NO$ $[M+H]^+$: 230.1545. Found: 230.1547.

3.2.4. (1′S,4S)-4-(1-Bromo-2-methyl-propyl)-1-(1-phenyl-ethyl)-pyrrolidin-2-one (15)

The title compound was obtained as a diastereomeric mixture at C–Br atom in 70% yield. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 0.93 (d, 3H, *J*=6.6 Hz), 0.94 (d, 3H, *J*=6.6 Hz), 0.97 (d, 3H, *J*=3.9 Hz), 1.02 (d, 3H, *J*=6.9 Hz), 1.53 (d, 3H, *J*=7.2 Hz), 1.54 (d, 3H, *J*=7.2 Hz), 1.71–1.82 (m, 2H), 2.17 (dd, 1H, *J*=16.1, 10.8 Hz), 2.24 (dd, 1H, *J*=16.1, 9.9 Hz), 2.50 (dd, 1H, *J*=9.0, 2.4 Hz), 2.56 (dd, 1H, *J*=9.0, 2.4 Hz), 2.64 (m, 1H), 2.71–2.84 (m, 2H), 3.15–3.26 (m, 2H), 3.51 (m, 1H), 3.83 (dd, 1H, *J*=9.9, 3.3 Hz), 3.94 (dd, 1H, *J*=9.3, 3.3 Hz), 5.5 (m, 2H), 7.23–7.42 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 15.8, 15.9, 24.5, 24.7, 37.0, 37.2, 42.2, 42.5, 43.8, 46.5, 48.6, 48.8, 48.9, 52.4, 52.5, 127.0, 127.4, 127.5, 127.6, 128.4, 128.5, 128.6, 139.5, 139.6, 172.3. IR (CCl_4) *ν* 2965, 2853, 1688, 1422, 1249 cm^{-1}. FAB-HRMS *m/z* calcd for $C_{16}H_{23}BrNO$ $[M+H]^+$: 324.0963. Found: 324.0960.

3.3. Synthesis of (1R,2S)-CAMP (10)

3.3.1. (1′S,1R,5S)-3-(1-Phenyleth-1′-yl)-3-aza-bicyclo-[3.1.0]hexane-2-one (16)[14c]

To a solution of (1′*S*,4*S*)-**5**[7] (0.34 g, 1.2 mmol) in dry THF (30 mL) at 0 °C was added a solution of potassium *tert*-butoxide (2.4 mmol, 1 M solution in THF). The resulting solution was stirred for 1 h. The reaction mixture was quenched with 30 mL of water, and extracted with ethyl acetate (30 mL three times). The organic layer was dried with $NaSO_4$ and evaporate under reduced pressure and the residue was purified by column chromatography through silica gel (230–400 mesh) with hexane/EtOAc (v/v=8:1) to give 0.24 g of (1′*S*,1*R*,5*S*,)-**16** (98%) as colorless oil. $[\alpha]_D$ −96.5 (*c* 1.0, $CHCl_3$) (lit.[14c] $[\alpha]_D$ −160.8 (*c* 1.0, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$) *δ*: 0.55 (ddd, 1H, *J*=7.6, 4.4, 3.2 Hz), 1.09 (ddd, H, *J*=7.6, 4.8, 4.5 Hz), 1.40 (d, 3H, *J*=8.0 Hz), 1.74 (m, 1H), 1.93 (m, 1H), 3.05 (dd, 1H, *J*=10.4, 5.6 Hz), 3.19 (dd, 1H, *J*=10.4, 1.6 Hz), 5.38 (q, 1H, *J*=7.2 Hz), 7.25–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 11.4, 12.4, 16.4, 20.2, 44.2, 48.3, 126.7, 127.2, 128.3, 139.7, 174.4.

3.3.2. (1R,5S)-3-Aza-bicyclo[3.1.0]hexan-2-one (18)[14c]

A solution of (1′*S*,1*R*,5*S*,)-**16** (0.38 g, 1.90 mmol) in 30 mL of THF was added dropwise to a deep blue solution of Li (0.1 g) in condensed NH_3 (20 mL) at −78 °C. The reaction mixture was allowed to stir for 1 h at −78 °C before the addition of an aqueous solution of NH_4Cl (40 mL), then the reaction mixture was neutralized with a diluted solution of HCl, extracted with ethyl acetate, dried with Na_2SO_4, and evaporated under reduced pressure. The reaction was purified by column chromatography through silica gel (230–400 mesh) with hexane/EtOAc (v/v=1:1) to give 0.2 g of (1*R*,5*S*)-**18** (96%) as a white solid. Mp=108–109 °C (lit.[14c] 106–109 °C). $[\alpha]_D$ +51.9 (*c* 1,

$CHCl_3$) (lit.[14c] $[\alpha]_D$ +49.2 (*c* 1, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.68 (dd, 1H, *J*=7.6, 4.5 Hz), 1.10 (ddd, 1H, *J*=9.0, 8.4, 4.4 Hz), 1.80 (m, 1H), 1.94 (m, 1H), 3.35 (br d, 1H, *J*=10.4 Hz), 3.52 (dd, 1H, *J*=10.4, 6.0 Hz), 6.01 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.2, 14.7, 19.3, 44.2, 179.3.

*3.3.3. (1R,2S)-2-(Aminomethyl)cyclopropanecarboxylic acid (**10**)*

A solution of (1*R*,5*S*)-**18** (0.15 g, 2.1 mmol) in 20 mL of HCl (1 M) was stirred at 70 °C for 8 h. The resulting solution was evaporated under reduced pressure and the residue was crystallized with a solution mixture of AcOEt/methanol (v/v= 1:5) to give 0.12 g of (1*R*,2*S*)-**10** as a white solid (80% yield). Mp=240–250 °C (lit.[14c] 239–241 °C). $[\alpha]_D$ −32.6 (*c* 1, H_2O) (lit.[14c] $[\alpha]_D$ −38.5 (*c* 0.99, 1 M HCl)). ^1H NMR (400 MHz, D_2O); δ: 0.94 (ddd, 1H, *J*=7.2, 5.6, 5.2 Hz), 1.20 (m, 1H), 1.53 (ddd, 1H, *J*=8.4, 7.6, 5.1 Hz), 1.80 (m, 1H), 3.14 (t, 2H, *J*=8.0 Hz). ^{13}C NMR (100 MHz, D_2O) δ: 13.0, 17.7, 17.9, 38.2, 176.7. IR (KBr) ν 3383, 1575, 1424, 1053 cm^{-1}.

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