Synthesis and 1,3-Dipolar Cycloadditions of Two New Chiral Geometrically Fixed α-Alkoxycarbonylnitrones from a Single Chiral Source

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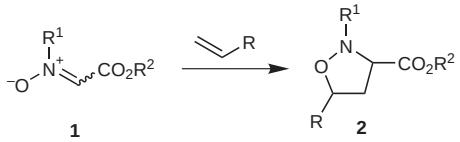
Abstract: The synthesis and 1,3-dipolar cycloaddition reactions of two new camphor-derived nitrones are described. These two nitrones reacted with alkenes in high yield and with high stereoselectivity. The chemical transformations of the cycloadducts were also examined.

Key words: 1,3-dipolar cycloadditions, chiral nitrone, stereoselectivity, chiral auxiliaries, asymmetric synthesis

Asymmetric 1,3-dipolar cycloaddition reactions between nitrones and alkenes are among the most efficient methods for the construction of optically active isoxazolidines, which are readily converted to synthetically useful chiral γ-amino alcohols (Scheme 1).[1] In particular, intermolecular 1,3-dipolar cycloaddition of α-alkoxycarbonylnitrones **1** is very attractive for construction of various nitrogen-containing carbon frameworks because of the high reactivity of **1**. However, nitrones **1** are known to exist as equilibrating mixtures of *E*- and *Z*-configuration in solution even at room temperature.[2] As a result, cycloadditions of nitrones **1** with alkenes often gave mixtures of diastereomers.



Scheme 1

To control the geometry of nitrone **1**, several chiral *E*-geometry-fixed α-alkoxycarbonylnitrones have been prepared.[3] In our laboratory, for preparation of optically active α-amino acid, we have investigated two chiral glycine templates, tricycloiminolactone **4a** and **4b** derived from camphorquinone.[4] Alkylation of **4a** and **4b** afforded the α-monosubstituted product in good yield and excellent diastereoselectivities. Hydrolysis of the product provided D- and L-α-amino acid (Scheme 2). Herein we describe the preparation and evaluation of two new chiral six-membered ring nitrones **6** and **10**.[1]

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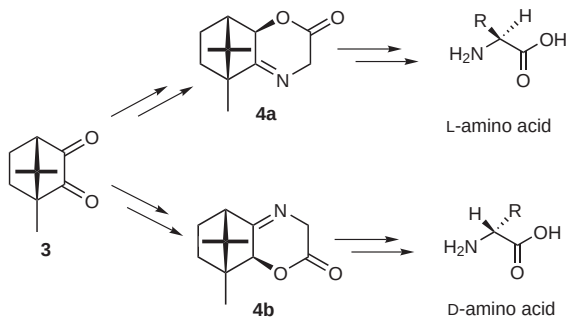
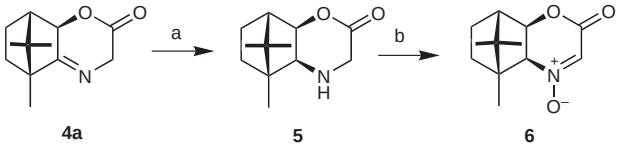


Scheme 2

Nitrone **6** was prepared from the tricycloiminolactone **4a** in a two-step procedure (Scheme 3). Hydrogenation of **4a** in the presence of 10% Pd/C in *i*-PrOH gave amine **5** in a quantitative yield.[5]

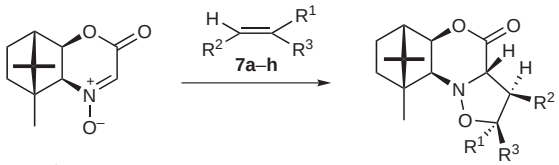
To obtain nitrone **6**, several oxidation methods were attempted. Oxidation of **5** with Na_2WO_4–H_2O_2,[6a] SeO_2–H_2O_2,[6b] methyltrioxorheniumurea–hydrogen peroxide complex,[3a,e] or dimethyl dioxirane gave a low yield of **6** (<23%), probably because nitrone **6** was more reactive, and overoxidation was a significant problem. Eventually, oxidation of **5** in the presence of MCPBA/Na_2CO_3 afforded **6** in a better yield (44%).[7]



Scheme 3 *Reagents and conditions*: a) 10% Pd/C, *i*-PrOH, r.t., 100%; b) MCPBA, Na_2CO_3, 0 °C to r.t., 44%.

With the cyclic nitrone **6** in hand, we next examined its reactivity and stereoselectivity in cycloadditions. Nitrone **6** underwent cycloaddtion reactions with a wide range of alkenes. The reactions occurred with the normal regiochemical outcome as expected for cycloadditions of this type to produce the cycloadducts in high yield (95–100%, Table 1).[8] Hence, cycloadditions of **6** with alkenes (**7a**–**d**,**g**,**h**) gave the α-face cycloadducts (**8a**–**d**,**g**,**h**) in high *exo*/*endo* ratio (>20:1 to >99:1, Table 1). Although the *exo*/*endo* selectivities between nitrone **6** with allylic alcohol **7e** and with α-methylstyrene **7f** were less satisfactory (5:1 and 5:2, respectively), the cycloadducts were also produced as the all α-face diastereomers.

Table 1 Cycloadducts **8a–h** Obtained from the 1,3-Dipolar Cycloadditions of **6** to Alkenes **7a–h**



Alkene	R^1	R^2	R^3	Conditions	Yield (%)[a,b]	*exo*/*endo*[c]
7a	H	H	Ph	60 °C, 8 h	98	>99:1
7b	H	H	Bu	60 °C, 32 h	95	>20:1
7c	H	$-(CH_2)_4-$		60–80 °C, 89 h	100	>99:1
7d	H	$-(CH_2)_3-$		30 °C, 25 h	99	>99:1
7e	H	H	CH_2OH	60 °C, 5 h	100	5:1
7f	Ph	H	Me	60 °C, 67 h	100	5:2
7g	CO_2Me	H	Me	60 °C,15 h	100	>20:1
7h	H	$-(o\text{-}CH_2C_6H_4)-$		60 °C, 25 h	100	>20:1[d]

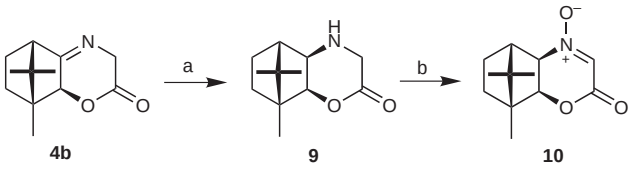
[a] Reactions were performed using 10 equiv of alkene in toluene. The structure of the major isomer is shown.
[b] Total yield of *exo* and *endo* isomers (purified major isomer).
[c] The *exo* assignment refers to the 5-alkyl or aryl substituent (for **8f** and **8g**, *exo* refers to 5-methyl). The stereochemistry of **8a**–**h** was determined by 1D NOE. The *exo*/*endo* ratio was determined by integration of ^{1}H NMR (400 MHz) spectra of the crude reaction mixture.
[d] Major isomer was not isolated in pure form.

In all cases studied, the stereochemical outcome of the cycloaddition reactions was the result of reaction from the less hindered α-face of nitrone **6** and this placed the isoxazolidine 5-substituent (R^3) of the major stereoisomer in the *exo* position. The α-face selectivity of the cycloadditions was similar to what was previsouly reported by us,[4a] in which the tricycloimnolactone **4a** afforded the α-monosubstituted products in excellent diastereoselectivities (de >98%). This was due to the steric hidrance of C_{12}-methyl group which effectively blocked the approach to the β-face and thus favored the attack of electrophile from the α-face of the enolate. A similar stereochemical course was also described by Tamura.[3b]

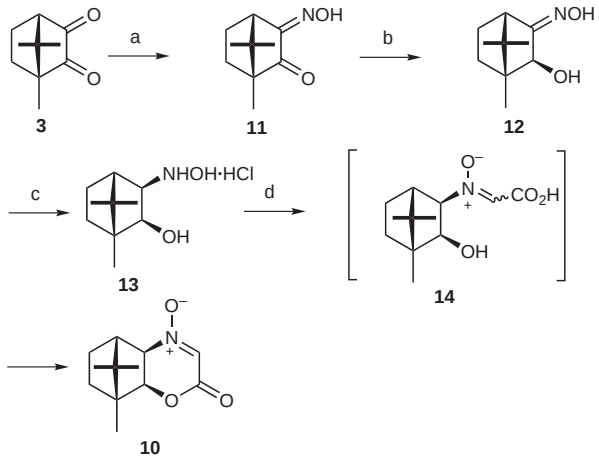
Because of steric hindrance between the substituents on the alkenes and the nitrone **6**, *exo* transition states were favored, and 5-*exo*-substituted isoxazolidines were the major isomers. For methyl methacrylate **7g**, interaction between the N^+–O^- bond of nitrone **6** and the C=O bond of **7g** favored the formation of the major cycloadduct **8g**.[3f]

The successful application of **6** in cycloaddition reactions prompted us to examine the usefulness of the regioisomeric nitrone **10** for this kind of reaction. Similar to the preparation procedure of **6** (Scheme 4), hydrogenation of **4b** proceeded in high yield to give compound **9**, but its oxidation to nitrone **10** was not satisfactory (9%).

Optimizations were therefore conducted to find a satisfactory method for nitrone **10** (Scheme 5). Condensation of 3-(hydroxyamino)isoborneol hydrochloride **13**[9] with

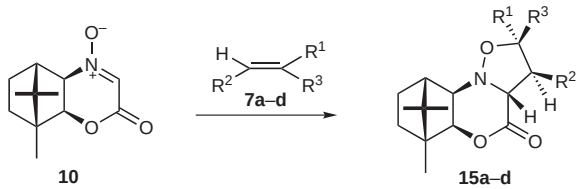


Scheme 4 *Reagents and conditions*: a) 10% Pd/C, *i*-PrOH, r.t., 100%; b) MCPBA, Na_2CO_3, 0 °C to r.t., 9%.



Scheme 5 *Reagents and conditions*: a) NH_3OHCl, AcONa, EtOH–H_2O, reflux, 2 h; b) $NaBH_4$, EtOH; c) $NaBH_3CN$, MeOH, pH 3–4; d) 50% $CHOCO_2H$ (aq), $NaHCO_3$, then TsOH, reflux, then DCC, r.t.

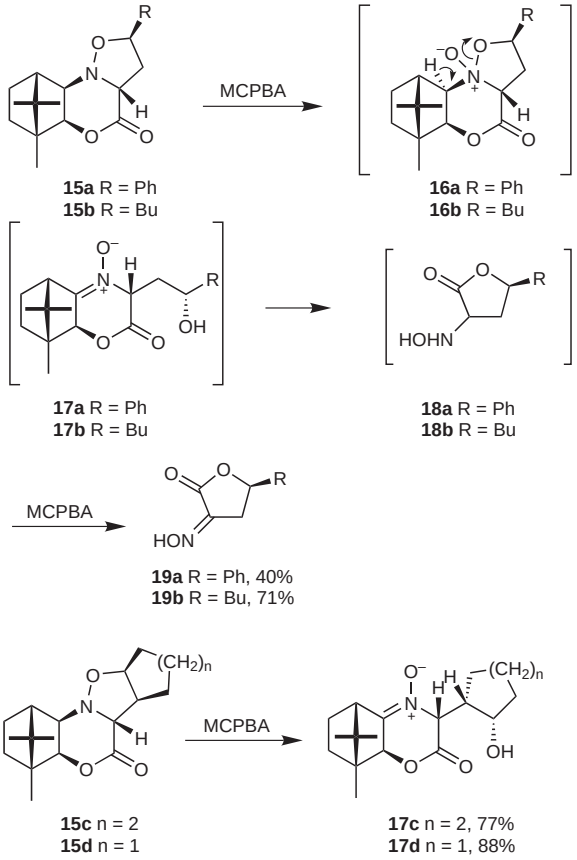
Table 2 Cycloadduts **15a–d** Obtained from the 1,3-Dipolar Cycloadditions **10** to Alkenes **7a–d**



Alkene	R^1	R^2	R^3	Conditions	Yield (%)[a,b]	*exo*/*endo*[c]
7a	H	H	Ph	60 °C, 19 h	100	>20:1
7b	H	H	Bu	60 °C, 19 h	99	>20:1
7c	H	$-(CH_2)_4-$		30 °C, 77 h	93	>99:1
7d	H	$-(CH_2)_3-$		30 °C, 46 h	99	>99:1

[a] Reactions were performed with 10 equiv of alkene in toluene. The structure of the major isomer is shown.
[b] Total yield of *exo* and *endo* isomers (purified major isomer).
[c] The *exo* assignment refers to the 5-alkyl or aryl substituent. The stereochemistry of **15a–d** was determined by 1D NOE. The *exo*/*endo* ratio was determined by integration of ^{1}H NMR (400 MHz) spectra of the crude reaction mixture.

glyoxylic acid and in situ cyclization of the nitrone intermediate **14** with TsOH gave the target nitrone **10** in 37% yield.[3b] This yield could be improved to 50% by using TsOH–DCC for the cyclization.[10]



Scheme 6 *Reagents and conditions*: MCPBA (3.5 equiv), CH_2Cl_2, 0 °C to r.t., then 10% $Na_2S_2O_3$, 5% Na_2CO_3.

As expected, the 1,3-dipolar cycloadditions of the regioisomeric nitrone **10** with various alkenes **7a–d** gave **15a–d** in high yield and in high *exo*/*endo* ratio (>20:1 to 99:1, Table 2).[11]

To remove the camphor-derived chiral auxiliary group in the cycloadducts **8a–h** and **15a–d**, it is necessary to cleave the N–O and C–N bonds regioselectively. The cycloadducts were subjected to the oxidative procedure developed by Langlois.[12] However, treatment of **8a** with MCPBA failed to initiate any reactions, and only starting material was recovered. It was believed that the bridgehead methyl group adjacent to the nitrogen atom that blocked the approach of MCPBA. On the other hand, oxidation of the regioisomeric adduct **15a** with MCPBA afforded an intermediate *N*-oxide **16a** which underwent a spontaneous elimination to produce nitrone **17a**. Subsequent transesterification, hydrolysis and further oxidation of **17a** gave the α-oximino-γ-lactone **19a**. Similarly, the cycloadduct **15b** obtained from terminal alkene **7b** gave **17d** (Scheme 6).[13] For the cycloadducts **15c** and **15d**, similar oxidation gave nitrones **17c** and **17d**.[14] In this case, further hydrolysis and oxidation of **17c** and **17d** were not observed.

In summary, two new camphor-derived nitrones **6** and **10** were prepared. The 1,3-dipolar cycloadditions of **6** and **10** with a wide range of alkenes gave cycloadducts in high yield and excellent diastereoselectivities. Furthermore, oxidation of the cycloadducts **15a–d** led to derivatives **19a**, **19b** and **17c**, **17d** that may be useful in other organic syntheses.

Acknowledgment

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(5) Catalytic hydrogenation of **4a** in MeOH was also attempted. However, the mixture of compound **5** and a by-product which arised from transesterification of **4a** and MeOH were observed.

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(7) **Typical Procedure for the Preparation of Nitrone 6.**
To a solution of amine **5** (300 mg, 1.43 mmol) in CH_2Cl_2 (12 mL) was added a sat. aq Na_2CO_3 (18 mL). The resulting mixture was stirred at 0 °C. During this period, a solution of MCPBA (767 mg, 4.22 mmol) in CH_2Cl_2 (18 mL) was added dropwise over 1 h. After further stirring at r.t. for 12 h, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and filtered. Evaporation of the solvents gave a residue which was chromatographed over silica gel to afford the nitrone **6**; mp 126 °C (dec.); $[\alpha]_D^{23}$ –280 (*c* 0.51, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.16 (br s, 1 H), 4.78 (d, *J* = 8.1 Hz, 1 H), 3.86 (d, *J* = 8.1 Hz, 1 H), 2.30 (d, *J* = 4.8 Hz, 1 H), 1.89 (m, 1 H), 1.65 (m, 1 H), 1.30 (m, 1 H), 1.15 (m, 1 H), 1.15 (s, 3 H), 0.96 (s, 3 H), 0.91 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.15, 124.56, 81.06, 75.48, 52.09, 50.38, 48.38, 36.46, 22.77, 21.82, 19.85, 12.66. MS (EI): *m/z* (%) = 223 (2) [M^+], 206 (3) [M – 15], 178 (88), 95 (100). HRMS (ESI): *m/z* calcd for $C_{12}H_{18}NO_3^+$ [M + 1]: 224.1281; found: 224.1277.

(8) **Representative Experimental Procedure for Cycloaddition Reactions with Nitrone 6.**
A solution of nitrone **6** (50 mg, 0.224 mmol) and styrene **7a** (2.24 mmol) in 7 mL of toluene was heated at 60 °C for 8 h. The mixture was then concentrated under reduced pressure; the ^{1}H NMR spectrum of the crude product indicated a diastereomeric ratio of >99:1. An analytical sample **8a** crystallized from EtOAc–PE (1:1) had a mp of 197–199 °C; $[\alpha]_D^{18}$ +118 (*c* 1.10, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.31 (m, 5 H), 5.41 (dd, *J* = 9.6, 3.6 Hz, 1 H), 4.53 (d, *J* = 8.4 Hz, 1 H), 4.34 (dd, *J* = 8.4, 7.8 Hz, 1 H), 2.93 (d, *J* = 8.4 Hz, 1 H), 2.69 (m, 1 H), 2.57 (m, 1 H), 2.11 (d, *J* = 4.8 Hz, 1 H), 1.86 (m, 1 H), 1.63 (m, 1 H), 1.20–1.00 (m, 2 H), 1.14 (s, 3 H), 1.00 (s, 3 H), 0.88 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.11, 139.61, 128.70, 128.38, 126.62, 82.89, 77.52, 67.58, 61.49, 49.97, 49.07, 47.25, 39.82, 34.71, 23.55, 21.26, 20.02, 11.40. MS (EI): *m/z* (%) = 327 (17) [M^+], 310 (0.5) [M – 17], 144 (11), 136 (8), 104 (100), 95 (23). HRMS (ESI): *m/z* calcd for $C_{20}H_{26}NO_3^+$ [M + 1]: 328.1907; found: 328.1908.
Compound **8b**: mp 86–87 °C; $[\alpha]_D^{17}$ +105 (*c* 0.62, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.43 (d, *J* = 8.4 Hz, 1 H), 4.40 (m, 1 H), 4.01 (dd, *J* = 12.3, 8.1 Hz, 1 H), 2.74 (d, *J* = 8.4 Hz, 1 H), 2.28 (m, 1 H), 2.22 (m, 1 H), 2.03 (d, *J* = 5.1 Hz, 1 H), 1.79 (m, 1 H), 1.70–1.40 (m, 3 H), 1.40–1.20 (m, 4 H), 1.15–0.95 (m, 2 H), 1.07 (s, 3 H), 0.93 (s, 3 H), 0.88 (m, 3 H), 0.83 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.66, 82.77, 76.08, 67.55, 60.88, 49.92, 48.90, 47.21, 36.37, 34.69, 34.19, 27.97, 23.52, 22.53, 21.23, 19.93, 13.90, 11.35. MS (EI): *m/z* (%) = 307 (14) [M^+], 292 (0.5) [M – 15], 250 (13), 222 (17), 136 (68), 95 (100). HRMS (ESI): *m/z* calcd for $C_{18}H_{30}NO_3^+$ [M + 1]: 308.2220; found: 308.2215.

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(10) **Typical Procedure for the Preparation of Nitrone 10.**
A mixture of an aq solution (50%) of glyoxylic acid (0.728 g, 4.92 mmol), 3-(hydroxyamino) isoborneol hydrochloride (0.990 g, 4.47 mmol) and $NaHCO_3$ (0.376 g, 4.47 mmol) in CH_2Cl_2 was stirred for 30 min at r.t. The water of the mixture was removed azeotropically for 4.5 h. Anhyd *p*-TsOH (0.387 g, 2.24 mmol) was added to the mixture, and the mixture was heated at reflux for 14.5 h. After cooling, DCC (0.453 g, 2.24 mmol) was added, and the mixture was stirred for 4 h at r.t. After cooling, the mixture was washed with H_2O, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel to afford nitrone **10** (0.502 g, 50%) as a crystalline solid: mp 117 °C (dec.); $[\alpha]_D^{14}$ +224 (*c* 1.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (br s, 1 H), 4.53 (d, *J* = 8.8 Hz, 1 H), 3.92 (d, *J* = 8.8 Hz, 1 H), 2.68 (d, *J* = 4.4 Hz, 1 H), 1.92 (m, 1 H), 1.70 (m, 1 H), 1.20 (m, 2 H), 1.10 (s, 3 H), 0.91 (s, 3 H), 0.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.93, 124.47, 83.91, 72.32, 51.06, 48.63, 47.65, 32.41, 26.12, 21.63, 19.38, 10.81. MS (EI): *m/z* (%) = 223 (3) [M^+], 206 (2) [M – 15], 162 (4), 135 (33), 95 (100). HRMS (ESI): *m/z* calcd for $C_{12}H_{18}NO_3^+$ [M + 1]: 224.1281; found: 224.1285.

(11) **Representative Spectroscopic Data.**
Compound **15a**: mp of 152–154 °C. $[\alpha]_D^{15}$ –156 (*c* 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 5.42 (dd, *J* = 10.0, 3.6 Hz, 1 H), 4.28 (m, 1 H), 4.25 (d, *J* = 8.4 Hz, 1 H), 3.02 (d, *J* = 8.4 Hz, 1 H), 2.68 (m, 1 H), 2.52 (m, 1 H), 2.16 (d, *J* = 4.4 Hz, 1 H), 1.80 (m, 1 H), 1.62 (m, 1 H), 1.11 (m, 2 H), 1.04 (s, 6 H), 0.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.95, 139.63, 128.67, 128.35, 126.45, 85.97, 77.93, 64.21, 61.37, 49.63, 49.56, 47.44, 39.36, 33.16, 25.63, 21.51, 20.14, 11.02. MS (EI): *m/z* (%) = 327 (0.9) [M^+], 283 (0.6), 104 (100), 95 (23). HRMS (ESI): *m/z* calcd for $C_{20}H_{26}NO_3^+$ [M + 1]: 328.1907; found: 328.1908.
Compound **15b**: oil; $[\alpha]_D^{15}$ –107 (*c* 2.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (m, 1 H), 4.22 (d, *J* = 8.4 Hz, 1 H), 4.03 (dd, *J* = 12.0, 8.0 Hz, 1 H), 2.87 (d, *J* = 8.4 Hz, 1 H), 2.35 (m, 1 H), 2.27 (m, 1 H), 2.12 (d, *J* = 4.0 Hz, 1 H), 1.80 (m, 1 H), 1.60 (m, 3 H), 1.33 (m, 4 H), 1.09 (m, 2 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 0.90 (t, *J* = 7.0 Hz, 3 H), 0.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.51, 85.81, 64.13, 60.83, 49.48, 49.44, 47.36, 35.96, 34.32, 33.09, 27.86, 25.57, 22.53, 21.47, 20.06, 13.89, 10.99. MS (EI): *m/z* (%) = 307 (13) [M^+], 250 (26), 224 (19), 136 (100), 121 (53), 84 (69). HRMS (ESI): *m/z* calcd for $C_{18}H_{30}NO_3^+$ [M + 1]: 308.2220; found: 308.2217.

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(13) Compound **19a**: oil, $[\alpha]_D^{15}$ –74 (*c* 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.38 (br s, 1 H), 7.45 (m, 3 H), 7.35 (m, 2 H), 5.72 (dd, *J* = 8.4, 6.0 Hz, 1 H), 3.60 (dd, *J* = 19.6, 8.4 Hz, 1 H), 3.03 (dd, *J* = 19.6, 6.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.56, 147.41, 138.73, 129.02, 125.44, 78.30, 32.63. MS (EI): *m/z* (%) = 191 (36) [M], 168 (2), 107 (100), 77 (81), 57 (63). HRMS (ESI): *m/z* calcd for $C_{10}H_{13}N_2O_3^+$ [M + NH_4]: 209.0921; found: 209.0925.
Compound **19b**: mp 75–77 °C; $[\alpha]_D^{15}$ –58 (*c* 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57 (br s, 1 H), 4.70 (m, 1 H), 3.21 (dd, *J* = 19.2, 8.1 Hz, 1 H), 2.68 (dd, *J* = 19.2, 5.1 Hz 1 H), 1.80 (m, 1 H), 1.70 (m, 1 H), 1.40 (m, 4 H), 0.92 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.41, 148.17, 77.87, 36.22, 30.12, 26.62, 22.28, 13.83. MS (EI): *m/z* (%) = 154 (9) [M – 17], 126 (10), 114 (100). HRMS (ESI): *m/z* calcd for $C_8H_{17}N_2O_3^+$ [M + NH_4]: 189.1234; found: 189.1231.

(14) Compound **17c**: mp 243 °C (dec.); $[\alpha]_D$ –9 (*c* 0.37, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.57 (s, 1 H), 4.46 (d, *J* = 11.7 Hz, 1 H), 4.22 (br s, 1 H), 3.97 (s, 1 H), 3.22 (d, *J* = 4.5 Hz 1 H), 2.10–1.30 (m, 12 H), 1.20 (m, 1 H), 1.10 (s, 3 H), 0.98 (s, 3 H), 0.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.06, 150.60, 81.47, 75.43, 65.07, 50.60, 50.05, 48.10, 41.42, 34.03, 32.09, 24.97, 24.22, 21.85, 19.81, 19.50, 19.26, 10.32. MS (EI): *m/z* = 321 (1) [M^+], 304(3), 276 (7), 260 (3), 248 (4), 223 (77), 55 (99), 41 (100). HRMS (ESI): *m/z* calcd for $C_{18}H_{28}NO_4^+$ [M + 1]: 322.2013; found: 322.2009.
Compound **17d**: mp 70–72 °C; $[\alpha]_D^{15}$ –31 (*c* 0.17, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.69 (d, *J* = 12.3 Hz, 1 H), 4.62 (s, 1 H), 4.60 (br s, 1 H), 4.33 (br s, 1 H), 3.23 (d, *J* = 4.5 Hz 1 H), 2.20–1.52 (m, 10 H), 1.39 (m, 1 H), 1.12 (s, 3 H), 1.00 (s, 3 H), 0.90 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.79, 150.33, 81.34, 73.17, 72.97, 50.88, 50.09, 48.13, 46.26, 34.08, 32.99, 26.92, 23.03, 21.78, 19.81, 19.25, 10.31. MS (EI): *m/z* = 307 (0.3) [M^+], 278 (1), 262 (4), 234 (3), 223 (29), 55 (81), 41 (100). HRMS (ESI): *m/z* calcd for $C_{17}H_{26}NO_4^+$ [M + 1]: 308.1856; found: 308.1849.