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Synthesis of isoxazoline *N*-oxides and its application in the formal synthesis of dehydroclausenamide

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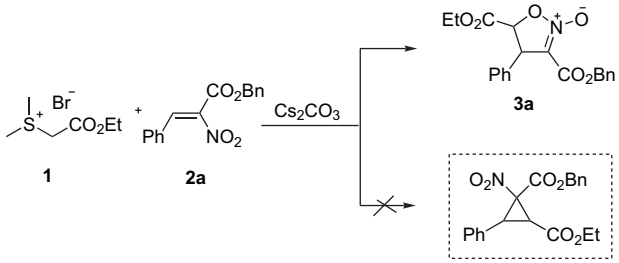
ABSTRACT

A protocol for the synthesis of isoxazoline *N*-oxides and its application in the formal synthesis of dehydroclausenamide are described. Sulfonium salt **1** reacts with substituted nitroalkenes smoothly to generate isoxazoline *N*-oxides in high to excellent yields with dr higher than 99/1. Its asymmetric version has been developed by using cinchona alkaloid-derived ammonium salts **6a** and **6b** instead of sulfonium salt **1** and higher than 96% ee values are achieved. This method has also been successfully applied to the formal synthesis of dehydroclausenamide.

1. Introduction

Isoxazoline *N*-oxides and their derivatives are frequently used as intermediates in the synthesis of complex molecules[1] and are found in several biologically active compounds.[2] Although many synthetic methods have been developed,[3] practical protocols for the enantioselective construction of isoxazoline *N*-oxides are very limited. The development of asymmetric synthesis of isoxazoline *N*-oxides with high diastereoselectivity and enantioselectivity remains a challengeable task.

In 1976, Holy reported that dimethylsulfoxonium methylide could react with nitroolefin to afford isoxazoline *N*-oxides in the presence of copper(I).[3a] Since this pioneering work, there have been several other studies on this reaction[3] but the product distribution (cyclopropane/isoxazoline *N*-oxide) was dependent on ylide and nitroolefins. As our on-going research project on ylide reaction[4] and its applications in organic synthesis, we found very recently that dimethylsulfonium salt **1** reacted with (*Z*)-benzyl 2-nitro-3-phenylacrylates **2** in the presence of K_2CO_3 leading to isoxazoline *N*-oxides **3** in high to excellent yields and no cyclopropane derivatives were observed in the reaction (Scheme 1). We communicated that, by using cinchonidine (cinchonine)-derived ammonium salts instead of the sulfonium salt, nitroolefins could be converted into optically active isoxazoline *N*-oxides with excellent ees and high drs.[5] This method has also been successfully applied to the formal synthesis of dehydroclausenamide. In this paper, we wish to report the results in details.



Scheme 1. Reaction of sulfonium salt **1** with nitroalkenes **2a**.

2. Results and discussion

2.1. Preparation of isoxazoline *N*-oxides through sulfonium ylide

Initially, it was found that dimethylsulfonium salt **1**, after deprotonation by Cs_2CO_3, reacted with (*Z*)-benzyl 2-nitro-3-phenylacrylate **2a**, affording isoxazoline *N*-oxide **3a** in 80% yield. Further studies showed that bases influenced strongly the yields. As shown in Table 1, K_2CO_3 gave the highest yield (91%), however, only 52% yield was obtained when KO^{t}Bu was employed as a base (entry 2, Table 1). In all the cases examined, the reaction proceeded well to give isoxazoline *N*-oxides exclusively with excellent diastereoselectivities in CH_3CN in the presence of both inorganic bases (Cs_2CO_3, K_2CO_3, KOH, and KO^{t}Bu) and organic base (^{i}Pr$_2$NH). No cyclopropane derivatives were detected.

Under the optimal conditions, we investigated the generality of the current reaction by evaluating with various nitroalkenes. As shown in Table 2, β-aryl, β-heteroaryl, and β-alkyl nitroalkenes were good substrates for this reaction to afford the desired

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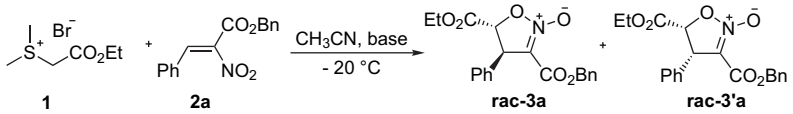
Table 1
Effects of bases on the cyclization[a]



Entry	Base	Yield[b] (*rac*-**3a**, %)	*rac*-**3a**/*rac*-**3′a**[c]
1	Cs_2CO_3	80	>99/1
2	K_2CO_3	91	>99/1
3	KOH	85	>99/1
4	$^{i}Pr_2NH$	89	>99/1
5	KO^{t}Bu	52	34/1

[a] Conditions: **2a** (57 mg, 0.2 mmol), base (0.3 mmol), and **1** (50 mg, 0.22 mmol) in CH_3CN (0.08 mol/L).
[b] Isolated yield.
[c] Determined by ^{1}H NMR.

products with excellent diastereoselectivities (>99/1) in high yields, providing an easy access to isoxazoline *N*-oxides. The *O*-substituent of ester groups influenced the yields slightly. For example, **2a** and **2b** gave the desired products in 91% and 99% yields, respectively (entries 1 and 2). Both the electronic and the steric properties of the aryl groups in nitroalkenes did not change the diastereoselectivities at all (entries 1–8). β-Alkyl nitroalkenes were also suitable substrates for this reaction with only a slight decrease in the yield. For all substrates evaluated, only the trans-isomers were obtained. Moreover, no cyclopropane derivatives were observed.

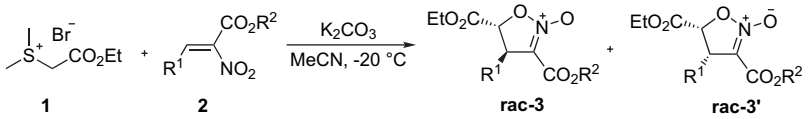
The products isoxazoline *N*-oxides were characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and mass spectroscopic techniques. Product **3a** was further confirmed by X-ray analysis (Fig. 1). The relative configuration of **3a** was determined by ^{1}H NMR as well as X-ray analysis, in which the phenyl group and the ethyl ester are located in trans-configuration.

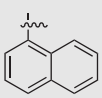
2.2. Asymmetric synthesis of isoxazoline *N*-oxides

Encouraged by the aforementioned results, we are interested in developing its asymmetric version of the present reaction. In view of the successful application of camphor-derived sulfonium ylides in enantioselective ylide reactions,[6,7] sulfonium salt **5** (Scheme 2) was first chosen for this purpose. As shown in Table 3, unfortunately, the reactions of salt **5** with nitroolefin **2a** only gave isoxazoline *N*-oxide **3a** with low ees and moderate des (entries 1–4) although the yields were quite good. Further studies showed that base influenced strongly the diastereoselectivities but did not improve the enantioselectivities (Table 3).

Gaunt and co-workers reported that cinchonidine (cinchonine)-derived ammonium salt **6a** was a good reagent for the synthesis of optical cyclopropane derivatives with high enantioselectivities.[8] Thus, we tried the asymmetric cyclization reaction by employing ammonium salt **6a** instead of sulfonium salt **5**. We are pleased to find that nitroalkenes could be converted smoothly into the corresponding optically active isoxazoline *N*-oxides with excellent des and ees when ammonium ylides derived from **6a** or **6b** was used. As summarized in Table 4, various 3-aryl-2-nitro-α,β-unsaturated esters prove to be good substrates for this cyclization. The *O*-substituent of the ester group influenced slightly the enantioselection (entries 1 and 2). Both 3-aryl and 3-heteroaryl-2-nitro acrylates worked smoothly, affording *trans*-isoxazoline *N*-oxides as single diastereomers. The enantiomeric excesses are nearly independent

Table 2
Reaction of salt **1** with nitroalkenes **2**[a]



Entry	R^1	R^2	Yield[b] (%)	*rac*-**3**/*rac*-**3′**[c]
1	Ph	Bn (**2a**)	91	>99/1
2	Ph	Me (**2b**)	99	>99/1
3	*o*-$MeOC_6H_4$	Me (**2c**)	88	>99/1
4	*p*-$MeOC_6H_4$	Bn (**2d**)	99	>99/1
5	*p*-MeC_6H_4	Bn (**2e**)	94	>99/1
6	*p*-FC_6H_4	Me (**2f**)	92	>99/1
7	*p*-BrC_6H_4	Me (**2g**)	98	>99/1
8		Bn (**2h**)	93	>99/1
9		Me (**2i**)	87	>99/1
10		Me (**2j**)	85	>99/1
11	*i*-C_3H_7	Me (**2k**)	79	>99/1

[a] Conditions: **2** (0.2 mmol), K_2CO_3 (42 mg, 0.3 mmol), and **1** (50 mg, 0.22 mmol) in CH_3CN (0.08 mol/L).
[b] Isolated yield of *rac*-**3**.
[c] Determined by ^{1}H NMR.

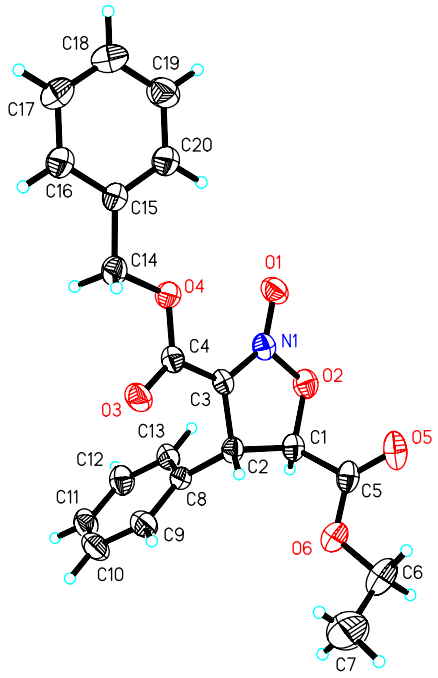
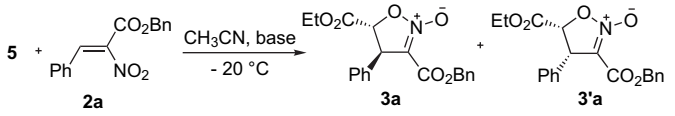


Figure 1. X-ray crystal structure of compound **3a**.

on the substituents of the aryl and heteroaryl groups. In all cases examined, trans-isomers of the desired products were obtained with higher than 96% ee in good yields (entries 1–11), providing an easy access to optically active isoxazoline *N*-oxides. Although both the yield and diastereoselectivity decreased, aliphatic nitroalkene **2k** was suitable for this cyclization and gave the desired product with 99% ee (entry 12). Noticeably, the same cyclization underwent smoothly using cinchonine-derived salt **6b** instead of **6a**, affording the desired product in 99% ee with opposite configuration (entries 2 and 3). Thus, both enantiomers could be obtained easily just by a simple choice of the ammonium salts. When salts **6c** and **6d** were used, both the desired isoxazoline *N*-oxide and cyclopropanes were not observed (entries 13–14).

Under basic conditions, the reactions of salts **6a** and **6b** with 2-nitro-α,β-unsaturated esters afford *trans*-isoxazoline *N*-oxides predominantly with excellent ees and diastereoselectivities. Generally, the selectivities of ylide cyclization depend on the degree of the reversibility and the stereochemical course of the Michael addition reaction. Nitrogen ylide is regarded to be more active than the corresponding sulfur ylide.[9] Aggarwal and co-workers have demonstrated that amine is a poorer leaving group than dimethyl sulfide since C–N bond is stronger than C–S bond[10] in a number of elegant studies on ylide epoxidation.[7c,e,11] Based on these mechanism insights, together with the highly electron-deficient nature of the substrate, it is envisaged that the intramolecular substitution might be the rate-determining step (Scheme 3). Since the intermediate **A** is more stable than **B** due to steric effects, trans-isomer is formed predominantly. To further understand the

Table 3
Reaction of salt **5** with nitroalkenes **2**[a]

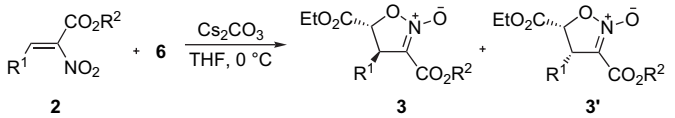


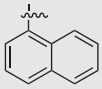
Entry	Base	**3a**/**3′a**[b]	Yield[c] (%)	ee[d] (%)
1[e]	Cs_2CO_3	9/1	89	26
2[f]	Cs_2CO_3	12/1	88	27
3[e]	K_2CO_3	4/1	92	39
4[e]	DBU	8/1	93	33

[a] Conditions: **2a** (57 mg, 0.2 mmol), base (0.22 mmol), and **5** (80 mg, 0.22 mmol) in CH_3CN (0.08 mol/L).
[b] Isolated total yield of **3a** and **3′a**.
[c] Determined by ^1H NMR.
[d] Determined by chiral HPLC for trans-isomer.
[e] dr of **5** was 8.7/1.
[f] dr of **5** was 12.4/1.

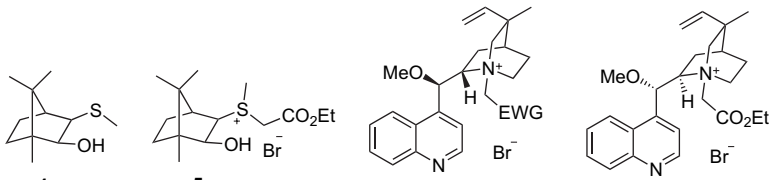
mechanism, we tried to develop single crystal of ylide derived from **6a** but failed. X-ray analysis of salt **6a** showed that quinolinyl group shields one face of the ester group as well as the pre-ylidic carbon

Table 4
Reaction of ammonium salts **6** with nitroalkenes **2**[a]

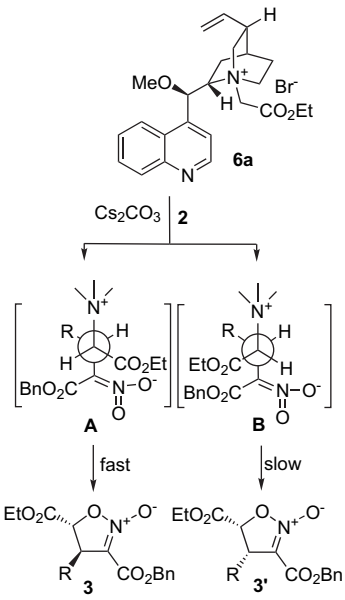


Entry	R^1	R^2	**6**	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	Bn (**2a**)	**6a**	65	>99/1	>99
2	Ph	Me (**2b**)	**6a**	62	>99/1	97
3	Ph	Me (**2b**)	**6b**	69	>99/1	−99
4	*o*-$MeOC_6H_4$	Me (**2c**)	**6a**	54	>99/1	99
5	*p*-$MeOC_6H_4$	Bn (**2d**)	**6a**	75[e]	>99/1	99
6	*p*-MeC_6H_4	Bn (**2e**)	**6a**	77	>99/1	97
7	*p*-FC_6H_4	Me (**2f**)	**6a**	79	>99/1	99
8	*p*-BrC_6H_4	Me (**2g**)	**6a**	74	>99/1	98
9		Bn (**2h**)	**6a**	67	>99/1	>99
10		Me (**2i**)	**6a**	79	>99/1	>99
11		Me (**2j**)	**6a**	68	>99/1	96
12	*i*-C_3H_7	Me (**2k**)	**6a**	30[f]	80/20	99
13	*p*-MeC_6H_4	Me (**2l**)	**6c**	0	—	—
14	*p*-MeC_6H_4	Me (**2l**)	**6d**	0	—	—

[a] Conditions: **2** (0.2 mmol), Cs_2CO_3 (72 mg, 0.22 mmol), **6** (0.22 mmol) in THF (0.08 mol/L); and H_2O (10 μL).
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Determined by chiral HPLC for trans-isomer.
[e] Cinchonidine-derived amine was recovered at the yield of 59%.
[f] Total yield of **3k** and **3k′**.



Scheme 2. Precursors of chiral ylides in the asymmetric reactions with nitroalkenes.



Scheme 3. A proposed mechanism.

(Fig. 2). We assumed that the conformation of the corresponding ylide in solution is similar to that of salt **6a** and so a possible stereochemical model was proposed to explain the enantioselectivity. As shown in Figure 2, the nitroolefin can only approach to the *si*-face of the ylide due to the steric hindrance by the quinolinyl group and the bicyclic ring, which forms stable intermediate **A** and lead to (*R*,*R*)-isoxazoline *N*-oxides[12] as the major products, which are consistent with the observed result. A clear mechanistic understanding waits for further investigation.

2.3. Formal synthesis of dehydroclausenamide

Dehydroclausenamide **11**[13] a potentially hepatoprotective amide,[14] was isolated from dry leaves of Chinese folk medicine Clausena lansium. It was found that product *ent*-**3b** could be employed for the formal synthesis of this compound. As shown in Scheme 4, by exposure to trimethylphosphite, *ent*-**3b** was deoxygenated to isoxazoline **7** in 90% yield.[15] The isoxazoline was treated with Raney Ni under H_2 atmosphere to form lactam **8**.[16] Methylation of the lactam, followed by reaction with PhLi[17] gave phenylketone **10**, which could be easily transformed into dehydroclausenamide **11** in two steps according to literature.[13b] Compound **10** was fully characterized by ^1H, ^{13}C NMR, and further confirmed by an X-ray crystallographic analysis (Fig. 3).[18] The rotation $[\alpha]_D^{20}$ (*c* 0.97, $CHCl_3$) of compound **10** was −116.5°, slightly higher than that reported in literature [−111.7 (*c* 1.00, $CHCl_3$)],[13c] suggesting that there is almost no loss of optical purity in the aforementioned transformations (Scheme 4). Thus, the enantioselective total synthesis of dehydroclausenamide **11** could be finished in seven steps using nitroolefin **2b** as a starting material.

3. Conclusions

We have developed a highly efficient ylide cyclization for the synthesis of optically active isoxazoline *N*-oxides by the reaction of

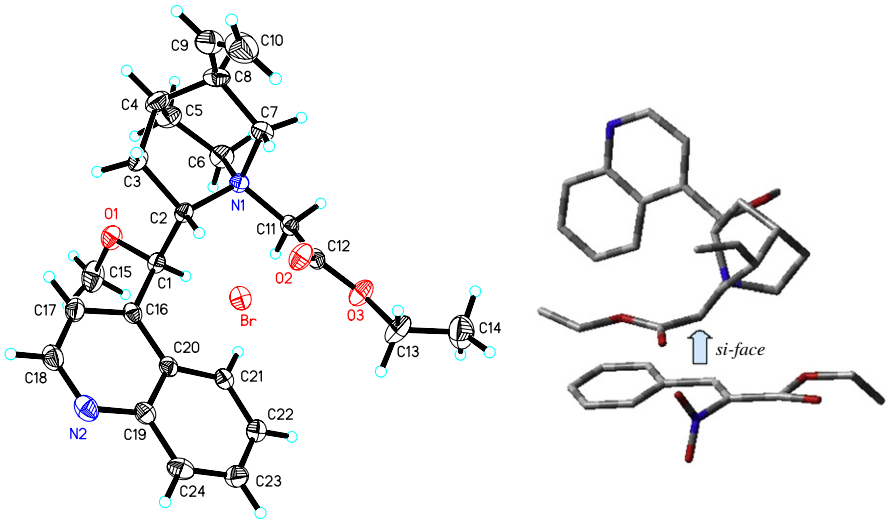
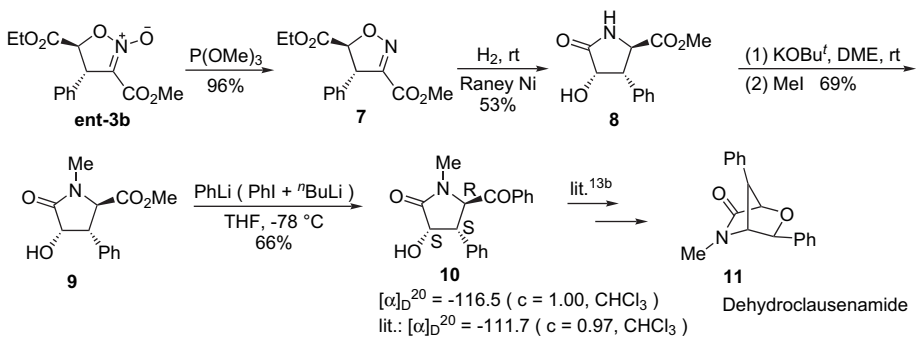


Figure 2. Molecular structures of salt **6a** and a possible stereochemical model.



Scheme 4. Formal synthesis of dehydroclausenamide **11**.

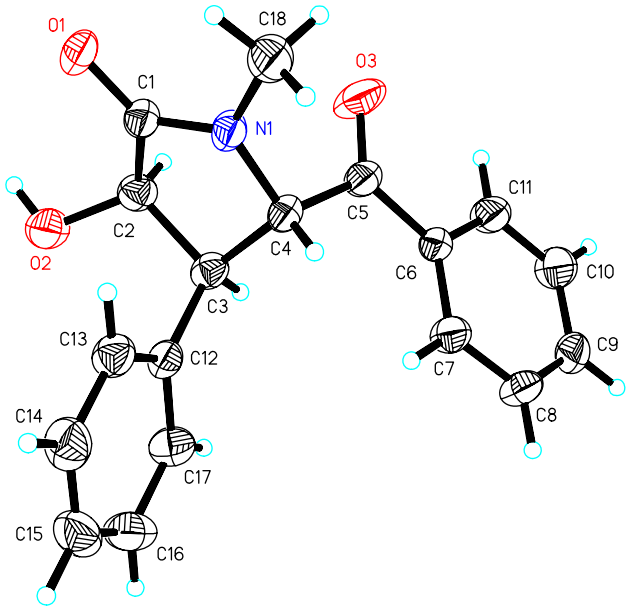


Figure 3. Single-crystal X-ray diffraction analysis of compound **10**.

sulfur or ammonium salts with nitroalkenes. By employing cinchonidine (cinchonine)-derived ammonium salts instead of sulfur ylide, excellent enantioselectivities and diastereoselectivities could be achieved. Both enantiomers can be obtained just by a choice of cinchonidine-derived and cinchonine-derived ylides used. Although a stoichiometric amount of chiral reagent is used, cinchonidine and cinchonine are quite cheap and recoverable. This reaction has also been successfully applied to the formal synthesis of dehydroclausenamide. The high diastereoselectivity, the excellent enantioselectivity, the easily accessible, and the cheap starting material make this reaction practically useful.

4. Experimental section

4.1. General procedure for the reaction of sulfonium salt 1 and nitroalkenes 2: (2a–2k)

A solution of salt **1**[2] (51 mg, 0.22 mmol) and nitroalkene **2** (0.2 mmol) in MeCN (2.5 mL) was cooled to −20 °C under N_2. To the solution was added K_2CO_3 (42 mg, 0.30 mmol) and then the reaction mixture was stirred at −20 °C for the desired time. After the reaction was complete (monitored by TLC), the mixture was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), washed with AcOEt (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/petroleum ether/Et_3N, v/v/v, 100/500/1.8).

4.2. General procedure for the ammonium ylide annulation reaction (substrates 2a–2k)

A mixture of salt **1** (0.22 mmol), Cs_2CO_3 (0.22 mmol), and nitroalkene **2** (0.2 mmol) was cooled to 0 °C under N_2. To the mixture were then added H_2O (10 μL) and THF (2.5 mL). The reaction mixture was stirred at 0 °C for the desired time. After the reaction was complete (monitored by TLC), the mixture was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), washed with AcOEt (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc/petroleum ether/Et_3N, v/v/v, 100/500/1.8).

Compound **3a** (solid): 46 h, 65% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_R (major)=12.75 min, t_R (minor)=20.94 min) gave the isomeric composition of the product: 99% ee. $[\alpha]_D^{20}$ −171.8 (*c* 1.11, $CHCl_3$). Mp 82–85 °C. IR (film) ν/cm^{-1} 3064 (m), 3033 (m), 2983 (m), 1743 (s), 1708 (s), 1635 (s), 1207 (m), 1148 (m), 750 (s), 699 (s). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.36–7.38 (m, 3H), 7.25–7.30 (m, 5H), 7.04–7.08 (m, 2H), 5.20 (ABd, *J*=12.3 Hz, 1H), 5.06 (ABd, *J*=12.3 Hz, 1H), 4.92 (d, *J*=3.0 Hz, 1H), 4.85 (d, *J*=3.0 Hz, 1H), 4.31 (q, *J*=7.2 Hz, 2H), 1.32 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 157.8, 137.8, 134.5, 129.3, 128.7, 128.4, 128.3, 127.9, 127.0, 108.8, 78.7, 67.2, 62.6, 52.5, 14.0. MS (ESI, *m*/*z*) 424.1 (M+MeOH+Na$^+$), 392.0 (M+Na$^+$), 387.1 (M+NH_4^+), 370.1 (M+H$^+$). Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 65.21; H, 5.19; N, 3.51.

Compound **3b** (solid):[3] 36 h, 62% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_R (major)=12.63 min, t_R (minor)=18.44 min) gave the isomeric composition of the product: 97% ee. $[\alpha]_D^{20}$ −228.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.27–7.43 (m, 5H), 4.93 (d, *J*=3.6 Hz, 1H), 4.84 (d, *J*=3.6 Hz, 1H), 4.33 (q, *J*=7.2 Hz, 2H), 3.75 (s, 3H), 1.35 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 158.6, 137.8, 129.4, 128.7, 126.9, 109.0, 78.7, 62.7, 52.7, 52.5, 14.0.

Compound *ent*-**3b** (solid): 36 h, 69% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R (minor)=15.09 min, t_R (major)=19.74 min) gave the isomeric composition of the product: −99% ee. $[\alpha]_D^{20}$ 216.0 (*c* 0.50, $CHCl_3$).

Compound **3c** (solid): 36 h, 54% yield, dr >99/1. HPLC analysis (Chiralcel AD-H, 10/90 ^{i}PrOH/hexanes, 0.4 mL/min, 238 nm; t_R (major)=28.02 min, t_R (minor)=38.33 min) gave the isomeric composition of the product: 99% ee. $[\alpha]_D^{20}$ −70.3 (*c* 1.13, $CHCl_3$). IR (film) ν/cm^{-1} 2956 (m), 2843 (m), 1741 (s), 1708 (s), 1632 (s), 1494 (m), 1246 (m), 1026 (m), 757 (s). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.33–7.35 (m, 1H), 7.12–7.14 (m, 1H), 6.94–6.98 (m, 2H), 5.15 (d, *J*=3.6 Hz, 1H), 4.86 (d, *J*=3.6 Hz, 1H), 4.30–4.34 (m, 2H), 3.88 (s, 3H), 3.74 (s, 3H), 1.35 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 158.8, 156.6, 129.9, 128.3, 125.2, 120.8, 111.0, 108.1, 78.0, 62.3, 55.5, 52.5, 47.9, 14.0. MS (ESI, *m*/*z*) 378.1 (M+MeOH+Na$^+$), 346.1 (M+Na$^+$), 324.1 (M+H$^+$). Anal. Calcd for $C_{15}H_{17}NO_7$: C, 55.73; H, 5.30; N, 4.33. Found: C, 55.79; H, 5.27; N, 4.33.

Compound **3d** (solid): 44 h, 65% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_R (major)=17.28 min, t_R (minor)=26.61 min) gave the isomeric composition of the product: 99% ee. Mp 87–90 °C. $[\alpha]_D^{20}$ −163.0 (*c* 1.02, $CHCl_3$). Mp 87–90 °C. IR (film) ν/cm^{-1} 2979 (m), 2904 (m), 2837 (m), 1738 (s), 1634 (s), 1538 (s), 1252 (m), 1030 (m), 838 (m), 754 (m), 698 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.26–7.30 (m, 3H), 7.21 (ABd, *J*=9 Hz, 2H), 7.11–7.12 (m, 2H), 6.88 (ABd, *J*=9.0 Hz, 2H), 5.22 (ABd, *J*=12 Hz, 1H), 5.09 (ABd, *J*=12 Hz, 1H), 4.89 (d, *J*=3.0 Hz, 1H), 4.80 (d, *J*=3.0 Hz, 1H), 4.31 (q, *J*=6.9 Hz, 2H), 3.82 (s, 3H), 1.33 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 159.9, 158.0, 134.6, 129.9, 128.5, 128.4, 128.3, 128.0, 114.7, 109.0, 79.0, 67.3, 62.6, 55.4, 52.0, 14.1. MS (ESI, *m*/*z*) 454.2 (M+MeOH+Na$^+$), 422 (M+Na$^+$), 417.3 (M+NH_4^+), 400.2 (M+H$^+$). Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.10; H, 5.12; N, 3.33.

Compound **3e** (solid): 37 h, 77% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.8 mL/min, 238 nm; t_R (major)=11.38 min, t_R (minor)=17.38 min) gave the isomeric composition of the product: 97% ee. $[\alpha]_D^{20}$ −137.7 (*c* 1.03, $CHCl_3$). Mp 82–83 °C. IR (film) ν/cm^{-1} 3032 (m), 2982 (s), 1738 (vs), 1709 (s), 1628 (vs), 1515 (m), 1456 (m), 1391 (m), 1361 (m), 1220 (s), 1024 (m), 818 (m), 751 (s), 698 (s). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.25–7.27 (m, 3H), 7.17 (s, 4H), 7.06–7.09 (m, 2H), 5.20 (ABd, *J*=12.0 Hz, 1H), 5.06 (ABd, *J*=12.0 Hz, 1H), 4.89 (d, *J*=3.0 Hz, 1H), 4.81 (d, *J*=3.0 Hz, 1H), 4.31 (q, *J*=6.9 Hz, 2H), 2.36 (s, 3H), 1.32 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 157.9, 138.6, 134.8, 134.5, 129.9, 128.3, 128.2,

127.9, 126.9, 108.9, 78.7, 67.2, 62.6, 52.2, 21.1, 14.0. MS (EI, *m*/*z*, rel intensity) 383 (M^+, 0.24), 91 (100.00). Anal. Calcd for $C_{21}H_{21}NO_6$: C, 65.79; H, 5.52; N, 3.65. Found: C, 65.82; H, 5.70; N, 3.48.

Compound **3f** (solid): 34 h, 79% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R (major)=14.96 min, t_R (minor)=20.54 min) gave the isomeric composition of the product: 99% ee. $[\alpha]_D^{20}$ −167.9 (*c* 0.94, $CHCl_3$). Mp 85–87 °C. IR (film) ν/cm^{-1} 2986 (m), 2938 (m), 1742 (s), 1631 (s), 1511 (s), 1443 (m), 1373 (m), 1229 (m), 977 (w), 841 (m), 756 (s). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.31–7.35 (m, 2H), 7.10 (t, *J*=8.4 Hz, 2H), 4.91 (d, *J*=2.7 Hz, 1H), 4.85 (d, *J*=2.7 Hz, 1H), 4.33 (q, *J*=7.2 Hz, 2H), 3.76 (s, 3H), 1.35 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 164.3 161.0, 158.5, 133.6, 133.5 (5), 128.8, 128.7, 116.5, 116.2, 108.8, 78.6 (5), 78.6 (3), 62.7, 52.7, 51.8, 14.0. MS (ESI, *m*/*z*) 366.2 ($M+MeOH+Na^+$), 334.2 ($M+Na^+$), 329.2 ($M+NH_4^+$), 312.2 ($M+H^+$). Anal. Calcd for $C_{14}H_{14}FNO_6$: C, 54.02; H, 4.53; N, 4.50. Found: C, 54.06; H, 4.44; N, 4.40.

Compound **3g** (solid): 34 h, 74% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R (major)=18.28 min, t_R (minor)=35.25 min) gave the isomeric composition of the product: 98% ee. $[\alpha]_D^{20}$ −162.3 (*c* 1.20, $CHCl_3$). Mp 88–90 °C. IR (film) ν/cm^{-1} 2978 (w), 2936 (w), 1740 (s), 1633 (s), 1442 (m), 1231 (s), 1011 (m), 756 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.54 (ABd, *J*=8.7 Hz, 2H), 7.23 (ABd, *J*=8.7 Hz, 2H), 4.89 (d, *J*=2.7 Hz, 1H), 4.83 (d, *J*=2.4 Hz, 1H), 4.33 (q, *J*=6.9 Hz, 2H), 3.76 (s, 3H), 1.35 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 158.4, 136.7, 132.5, 128.6, 122.8, 108.5, 78.3, 62.8, 52.8, 51.9, 14.0. MS (ESI, *m*/*z*) 428.1 ($M+2+MeOH+Na^+$), 426.1 ($M+MeOH+Na^+$), 396.0 ($M+2+Na^+$), 394.0 ($M+Na^+$), 391.0 ($M+2+NH_4^+$), 389.0 ($M+NH_4^+$), 374.0 ($M+2+H^+$), 372.0 ($M+H^+$). Anal. Calcd for $C_{14}H_{14}BrNO_6$: C, 45.18; H, 3.79; N, 3.76. Found: C, 45.28; H, 3.82; N, 3.61.

Compound **3h** (solid): 36 h, 67% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R=15.29 min, only one peak was observed) gave the isomeric composition of the product: >99% ee. $[\alpha]_D^{20}$ −84.4 (*c* 1.00, $CHCl_3$). IR (film) ν/cm^{-1} 3123 (w), 2983 (m), 1739 (s), 1633 (s), 1500 (m), 1456 (m), 1393 (m), 1224 (m), 747 (m), 698 (m), 598 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.22–7.39 (m, 6H), 6.35 (dd, *J*=1.5, 3.3 Hz, 1H), 6.27 (d, *J*=3.0 Hz, 1H), 5.26 (ABd, *J*=12.6 Hz, 1H), 5.14 (ABd, *J*=12.6 Hz, 1H), 5.04 (s, 2H), 4.30 (q, *J*=7.2 Hz, 2H), 1.31 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 157.7, 148.7, 143.1, 134.5, 128.4, 128.4, 128.0, 110.8, 108.4, 106.2, 76.0, 67.3, 62.7, 46.1, 13.9. MS (EI, *m*/*z*, rel intensity) 341 (M^+-H_2O, 1.01), 91 (100.00). HRMS (ESI) calcd for $C_{18}H_{17}NO_7Na^+$ ($M+Na^+$) 382.0901, found: 382.08973.

Compound **3i** (solid): 41 h, 79% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R (major)=14.71 min, t_R (minor)=20.79 min) gave the isomeric composition of the product: 99% ee. $[\alpha]_D^{20}$ −123.2 (*c* 1.10, $CHCl_3$). Mp 119–121 °C. IR (film) ν/cm^{-1} 3113 (w), 2993 (w), 2909 (w), 1740 (s), 1633 (s), 1438 (m), 1230 (m), 982 (m), 751 (s), 732 (m), 546 (w). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.32 (dd, *J*=0.9, 5.1 Hz, 1H), 7.09–7.10 (m, 1H), 7.02 (dd, *J*=3.6, 5.4 Hz, 1H), 5.18 (d, *J*=2.4 Hz, 1H), 5.05 (d, *J*=2.7 Hz, 1H), 4.33 (q, *J*=7.2 Hz, 2H), 3.80 (s, 3H), 1.35 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 158.3, 139.4, 127.4, 125.9 (9), 125.9 (6), 108.4, 78.8, 62.7, 52.7, 47.6, 13.9. MS (ESI, *m*/*z*) 354.1 ($M+MeOH+Na^+$), 322.1 ($M+Na^+$), 317.1 ($M+NH_4^+$), 300.1 ($M+H^+$). Anal. Calcd for $C_{12}H_{13}NO_6S$: C, 48.16; H, 4.38; N, 4.68. Found: C, 48.58; H, 4.05; N, 4.63.

Compound **3j** (solid): 39 h, 68% yield, dr >99/1. HPLC analysis (Chiralcel OD-H, 30/70 ^{i}PrOH/hexanes, 0.6 mL/min, 238 nm; t_R (major)=20.48 min, t_R (minor)=27.55 min) gave the isomeric composition of the product: 96% ee. $[\alpha]_D^{20}$ −3.0 (*c* 1.23, $CHCl_3$). IR (film) ν/cm^{-1} 3055 (w), 2981 (w), 2959 (w), 1759 (s), 1740 (s), 1633 (s), 1440 (s), 1227 (m), 1056 (w), 799 (m), 777 (m), 748 (m), 537 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 8.25 (d, *J*=8.4 Hz, 1H), 7.92 (d, *J*=0.9 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.65 (dd, *J*=6.3, 6.9 Hz, 1H), 7.58 (dd, *J*=6.3, 6.6 Hz, 1H), 7.46 (t, *J*=7.2 Hz, 1H), 7.32 (d, *J*=6.6 Hz, 1H), 5.72 (d, *J*=1.5 Hz, 1H), 4.88 (d, *J*=1.8 Hz, 1H), 4.38–4.44 (m, 2H), 3.72 (s, 3H), 1.41 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 158.7, 134.2, 132.8, 130.3, 129.4, 129.2, 127.1, 126.3, 125.4, 124.1, 122.5, 108.3, 78.5, 62.8, 52.8, 48.4, 14.0. MS (ESI, *m*/*z*) 398.1 ($M+MeOH+Na^+$), 366.1 ($M+Na^+$), 344.1 ($M+H^+$). Anal. Calcd for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found: C, 67.61; H, 4.94; N, 3.75.

Compound **3k** (oil): 39 h, 30% yield, dr=80/20. HPLC analysis (Chiralcel OD-H, 1/15 ^{i}PrOH/hexanes, 0.5 mL/min, 238 nm; t_{R1} (major)=28.16 min, t_{R1} (minor)=39.40 min, t_{R2} (major)=30.30 min, t_{R2} (minor)=33.59 min) gave the isomeric composition of the product: trans, 93% ee; cis, 88% ee. For trans-isomer: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 4.76 (d, *J*=2.7 Hz, 1H), 4.22 (dq, *J*=2.1, 6.9 Hz, 2H), 3.82 (s, 3H), 3.58 (dd, *J*=2.1 Hz, 3 Hz, 1H), 2.33 (hepta, *J*=3.9 Hz, 1H), 1.26 (t, *J*=7.8 Hz, 3H), 1.02 (d, *J*=7.2 Hz, 3H), 0.91 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.0, 108.3, 72.5, 62.2, 53.5 52.6, 29.2, 19.5, 16.6, 13.9. MS (EI, *m*/*z*, rel intensity) 242 (M^+-OH, 2.09), 186 (45.42), 144 (45.88), 142 (42.86), 100 (86.76), 85 (42.29), 59 (100.00), 43 (45.50), 41 (36.26). Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.40; H, 6.76; N, 5.20.

4.3. Procedure for the deoxygenation of *ent*-3b[15]

The starting material was dissolved in 4 mL/mmol of trimethyl phosphite in a flask equipped with a condenser and a thermometer. The mixture was stirred at 100 °C for 5 h under nitrogen, then diethyl ether was added (25 mL/mmol of starting material) and the solution was cooled to −10 °C, 1 N HCl (30 mL/mmol of starting material) was added to the mixture dropwise, extracted with diethyl ether (25 mL/mmol of starting material), washed with water (10 mL/mmol) and brine (5 mL/mmol). The organic layer was dried over sodium sulfate and concentrated in vacuo to give a crude product, which was purified by flash chromatography.

Compound **7** (solid): 90% yield. $[\alpha]_D^{20}$ 367.6 (*c* 0.95, $CHCl_3$). Mp 52–54 °C. IR (film) ν/cm^{-1} 3032 (w), 2984 (m), 2957 (m), 1735 (s), 1592 (m), 1497 (w), 1442 (m), 1456 (m), 1366 (m), 1230 (m), 1123 (m), 1023 (m), 915 (m), 792 (m), 752 (m), 700 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.20–7.37 (m, 5H), 5.07 (d, *J*=4.8 Hz, 1H), 4.84 (d, *J*=4.8 Hz, 1H), 4.28 (q, *J*=6.9 Hz, 2H), 3.78 (s, 3H), 1.32 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.7, 153.1, 136.7, 129.4, 128.5, 127.3, 87.8, 62.4, 56.4, 52.9, 14.0. MS (ESI, *m*/*z*) 332.2 ($M+MeOH+Na^+$), 300.2 ($M+Na^+$), 278.2 ($M+H^+$). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.43; H, 5.40; N, 4.83.

4.4. Procedure for the hydrogenation of 7[16]

A mixture of **7** (0.2 mmol) and Raney Ni (20 mg wet) in MeOH (2 mL) was subjected to H_2 (1 atm) at room temperature for 48 h. The catalyst was removed by filtration over Celite and the filtrate was concentrated. The residue thus obtained was subjected to column chromatography over silica gel (petroleum ether/AcOEt, 1:4) to afford **8**.

Compound **8** (solid): 25 mg, 53% yield. $[\alpha]_D^{20}$ −184.5 (*c* 0.50, $CHCl_3$). Mp 161–164 °C. IR (film) ν/cm^{-1} 3331 (w), 2920 (w), 1969 (w), 1732 (s), 1691 (s), 1438 (m), 1376 (m), 1216 (s), 789 (s), 700 (s). ^{1}H NMR (300 MHz, $(CD_3)_2SO$ with the internal dimethylsulfoxide signal at 2.5 ppm as a standard) δ 7.24–7.30 (m, 5H), 4.29 (d, *J*=4.5 Hz, 1H), 4.20 (d, *J*=7.2 Hz, 1H), 3.64 (s, 3H), 3.61 (d, *J*=4.8 Hz, 1H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$ with the internal dimethylsulfoxide signal at 39.5 ppm as a standard) δ 175.5, 172.2, 137.2, 128.9, 128.0, 126.9, 69.8, 58.5, 52.3, 49.3. MS (ESI, *m*/*z*) 290.2 ($M+MeOH+Na^+$), 258.2 ($M+Na^+$), 236.2 ($M+H^+$). Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.00; H, 5.68; N, 5.47.

4.5. Procedure for the methylation of 8

To a solution of **8** (0.2 mmol) in DME (2 mL) at 0 °C under nitrogen, was added KO^{t}Bu (0.24 mmol). After 2 min, MeI (0.3 mmol) was added. The resulting solution was stirred at room temperature for 24 h, then was passed rapidly through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh), washed with AcOEt (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/AcOEt, 1:2) to afford **9**.

Compound **9** (solid): 69% yield. Mp 115–117 °C. IR (film) ν/cm^{-1} 3347 (m), 1742 (s), 1714 (s), 1700 (s), 1684 (s), 1438 (w), 1398 (w), 1224 (m), 1085 (m), 765 (m), 735 (m), 700 (m). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.27–7.34 (m, 3H), 7.15–7.18 (m, 2H), 4.65 (dd, J=4.8, 7.8 Hz, 1H), 4.21 (d, J=2.1 Hz, 1H), 3.80 (s, 3H), 3.77–3.78 (m, 1H), 3.42 (d, J=4.8 Hz, 1H), 2.98 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 170.7, 136.2, 128.8, 128.1, 127.9, 70.3, 65.9, 52.8, 47.8, 29.4. MS (ESI, m/z) 304.1 (M+MeOH+Na$^+$), 272.2 (M+Na$^+$), 250.1 (M+H$^+$). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.31; H, 6.09; N, 5.47.

4.6. Procedure for the preparation of 10[17]

^{n}BuLi (0.33 mmol, 2.5 M in hexane) was added to a stirred solution of PhI (0.33 mmol) in THF (1 mL) at −78 °C. The resulting orange solution was then added dropwise to a solution of **6** (0.17 mmol) in THF (1 mL) at −78 °C. After 1 h, HCO_2Et (0.34 mmol) was added. And after 3 min of stirring at −78 °C, the reaction was quenched by adding silica gel (300–400 mesh, 0.5 g). The resulting mixture was passed through a glass funnel with a thin layer (20 mm) of silica gel (300–400 mesh) and washed with AcOEt (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/AcOEt, 1:1) to afford **10**.

Compound **10** (solid): 66% yield. $[\alpha]_D^{20}$ −116.5 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 7.86–7.89 (m, 2H), 7.64 (t, J=7.5 Hz, 1H), 7.49 (t, J=7.5 Hz, 2H), 7.37–7.40 (m, 3H), 7.20–7.36 (m, 2H), 5.09 (d, J=1.2 Hz, 1H), 4.57 (dd, J=4.8, 8.4 Hz, 1H), 3.73 (d, J=8.4 Hz, 1H), 3.10 (d, J=4.8 Hz, 1H), 3.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 174.5, 136.5, 134.4, 133.7, 129.0 (9), 129.0 (8), 128.5, 128.2, 128.1, 70.0, 69.0, 47.5, 29.6.

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Supplementary data

General synthetic procedures and characterization and spectral data for key compounds, CIF for compounds **3a**, **6a** and **10**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.075.

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18. For details, please see Supplementary data.