Introduction of the Acetate Unit to the 2-Pyridinone Ring System and Its Application to the Synthesis of (20*S*)-Camptothecin DE Ring System

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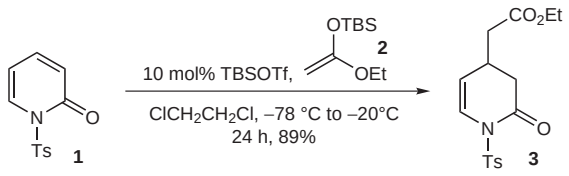
Abstract: The DE ring system of (20*S*)-camptothecin had been prepared from commercially available nicotinic acid in six steps utilizing the nucleophilic addition reaction of the silyl ketene acetal to the pyridinone ring as a key step.

Key words: anti-tumor agents, asymmetric synthesis, Lewis acids, nucleophilic additions, regioselectivity

The stereoselective construction of multi-functional piperidine ring systems through the use of pyridinium salts or dihydropyridine derivatives has been much investigated recently.[1,2] In particular, Comins and co-workers successfully applied the chiral 1-acyl-4-alkoxypyridinium salts to the syntheses of many biologically active natural products.[3] In comparison with the significant work on the 4-alkoxypyridine derivatives, research involving the reactivity of the 2-oxypyridine (2-pyridinone) derivatives has been limited mainly to Diels–Alder reactions.[4,5] To the best of our knowledge, the introduction of an acetate unit into oxygenated pyridine derivatives has been reported only once.[6]

As part of our continuous program for the development of new methodologies for heterocyclic compounds,[7] we focused our attention on the utilization of the activated 2-pyridinone derivatives. We have published the regioselective functionalization of *N*-tosyl-2-pyridinone (**1**)[5] with *tert*-butyldimethylsilyl ketene acetal **2**, activated by a Lewis acid (Scheme 1).[8]

(20*S*)-Camptothecin (**4**) is a well-known anti-cancer natural product that was first isolated from *Camptotheca acuminata* in 1966.[9,10] The first total synthesis of **4** was reported by Stork's research group as a racemate in 1971[11] and the first synthesis of the optically active form was carried out by Corey.[12] After the publication of the mechanism of the anti-cancer activities of **4**, which involved the interaction of **4** with DNA topoisomerase I,[13]



Scheme 1 Lewis acid catalyzed regioselective nucleophilic addition of silyl ketene acetal **2** to 2-pyridinone derivative **1**.

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camptothecin attracted many researchers and a large number of publications concerning the total synthesis of **4**[14–17] by unique methodologies have resulted. In spite of the fact that the D ring system of **4** is a substituted 2-pyridinone, there were no publications describing the straightforward synthesis of **4** using 2-pyridinone derivatives as the starting material. Here we report the short and efficient synthesis of the DE ring system of (20*S*)-camptothecin, an important intermediate in the synthesis of **4**, utilizing Lewis acid catalyzed functionalization of 2-pyridinone derivatives **5** (Figure 1).[16,17]

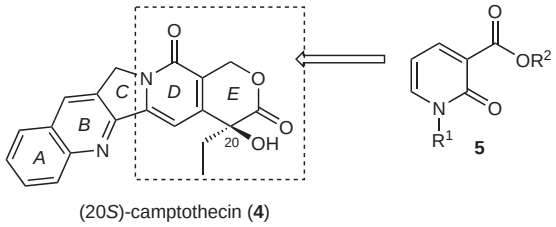


Figure 1

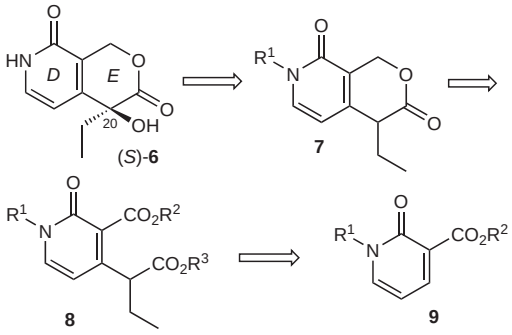
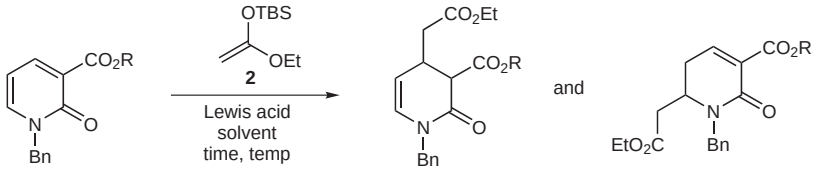


Figure 2 Retrosynthetic analysis for the preparation of the DE ring system of (20*S*)-camptothecin [(*S*)-**6**] from 2-pyridinone derivative **9**.

Our synthetic strategy is shown in Figure 2. The DE ring system (*S*)-**6** can be synthesized from **7** by enantioselective hydroxylation of the lactone, followed by removal of the protecting group (R^1). The lactone **7** can be constructed from **8** by the selective reduction of the alkoxycarbonyl group. The key reaction of this synthesis is the introduction of the butyrate unit into the 3-substituted-2-pyridinone derivative **9**.

Table 1 Reaction of 3-Alkoxycarbonyl-2-pyridinone Derivative **10a** or **10b** with Silyl Ketene Acetal **2**



10a: R = Me
10b: R = Bn

11a,**b** **12a**,**b**

Entry	Substrate (*R*)	Lewis acid (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)		
						11a or **11b** (dr)[a]	**12a** or **12b**	Recovered **10a** or **10b**
1	**10a** (Me)	TBSOTf (10)	DCE	–20	38	15 (13:1)	40	16
2		Et_2AlCl (110)	CH_2Cl_2	–40	2	40 (10:1)	11	31
3		Et_2AlCl (50)	CH_2Cl_2	–40	12	13 (14:1)	0	50
4	**10b** (Bn)	TBSOTf (15)	DCE	–20	27	13 (11:1)	36	51
5		Et_2AlCl (105)	CH_2Cl_2	–40	5	53 (10:1)	27	0

[a] Both **11a** and **11b** were isolated as a mixture of two inseparable diastereomers; the dr was measured by ^1H NMR spectroscopy.

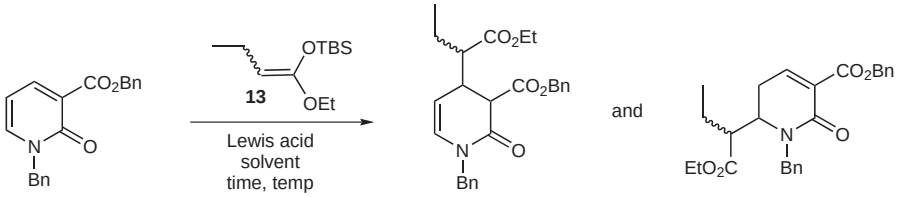
To clarify the reactivity of 3-alkoxycarbonylpyridione derivatives, the reactions between **10a** or **10b** and silyl ketene acetal **2** were examined and the results are summarized in Table 1.

From the results listed in Table 1, it is clear that a single electron-withdrawing group on the ring is enough to perform this reaction. The product ratios [**11a** (C4-adduct) vs **12a** (C6-adduct)] were inverted, depending on the Lewis acid used. Namely, TBSOTf catalyzed the reaction and gave **12a** as the major product (ca. 1:2.7, Table 1, entry 1), whereas Et_2AlCl gave **11a** preferentially (ca. 3.6:1, Table 1, entry 2), although a stoichiometric amount of Et_2AlCl was required to afford a reasonable yield of **11a** (Table 1, entry 2 vs 3). The other Lewis acids did not give satisfactory results (data not shown). The same tendency was observed for the benzyl ester **10b** (Table 1, entries 4 and 5), and the yield for **11b** was improved compared with the methyl ester **11a** (Table 1, entry 2 vs 5).

To apply this methodology to the synthesis of the DE ring system of camptothecin, the reactions between the TBS ketene acetal of ethyl butyrate and **10b** in the presence of either TBSOTf or Et_2AlCl were examined (Table 2).

Surprisingly, not only low yields, but also low selectivity between **14** and **15** and low diastereoselectivity for both compounds were observed for the addition reaction of (*E*)- and (*Z*)-TBS ketene acetal toward **10b** in the presence of TBSOTf (Table 2, entries 1 and 3). On the other hand, Et_2AlCl-mediated reactions were much more successful than those with TBSOTf, and apparent reversibility of the

Table 2 Reaction of 3-Alkoxycarbonyl-2-pyridinone Derivative **10b** with Silyl Ketene Acetal **13**



10b **14** **15**

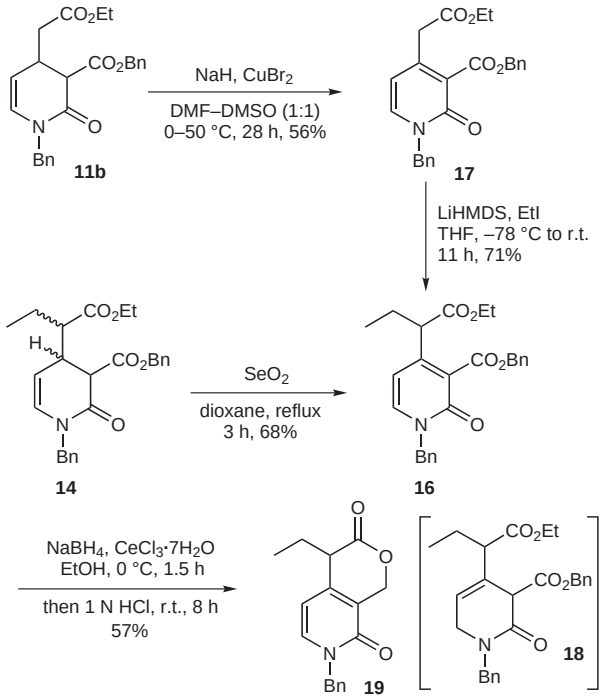
Entry	TBS ketene acetal **13**	Lewis acid (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)		
						14 (dr)[a]	**15** (dr)[a]	Recovered **10b**
1	(*E*)-**13**	TBSOTf (10)	DCE	–20	24	8 (1.1:1)	0	59
2		Et_2AlCl (105)	CH_2Cl_2	–40	2	68 (2:1)	11 (1:1.1)	8
3	(*Z*)-**13**	TBSOTf (10)	DCE	–20	24	10 (1:1.2)	7 (1.7:1)	73
4		Et_2AlCl (105)	CH_2Cl_2	–40	2	51 (1:4)	6[b]	32

[a] Both **14** and **15** were isolated as a mixture of two inseparable diastereomers; dr was measured by ^1H NMR spectroscopy.
[b] The dr was not determined.

diastereomeric ratio for **14** was observed depending on the geometry of TBS ketene acetal (Table 2, entry 2 vs 4). These results suggested that the reaction mechanism, especially the role of the Lewis acid, might differ between TBSOTf and Et_2AlCl. However, the details of the mechanism are not yet clear.

Consequently, the combination of **10b** and (*E*)-**13** as starting materials and Et_2AlCl as the Lewis acid afforded **14** with the best result among the tested compounds and conditions. Although **14** was isolated as a mixture of two kinds of diastereomers, both compounds are converted to the same 3,4-disubstituted-2-pyridinone in the next oxidation step. Thus, **14** was selected for the synthesis of the camptothecin DE ring system (*S*)-**6**.

Oxidation of **14** by SeO_2 in refluxing dioxane gave **16** in reasonable yield. Compound **16** was also synthesized from **11b** by oxidation with $CuBr_2$ in the presence of NaH[18] (56% yield) followed by alkylation of the lithium enolate of **17** with EtI in 71% yield. Selective reduction of the C3-benzyloxycarbonyl group was troublesome; for example, reduction by $NaBH_4$ gave **18** as the major product. This problem was finally resolved by employing the $NaBH_4/CeCl_3{\cdot}7H_2O$ system, and the lactone **19** was obtained in 57% yield after treatment with 1 N HCl (Scheme 2).

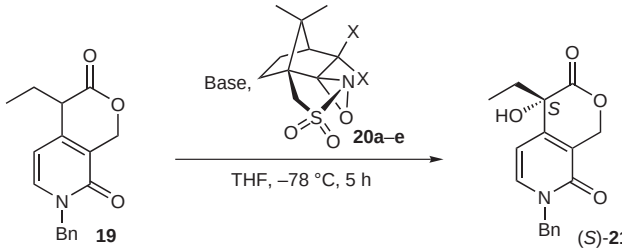


Scheme 2 Synthesis of the key intermediate **19** from 4-substituted lactam derivatives **11b** and **14**.

Asymmetric hydroxylation of 20-deoxycamptothecin has been reported by Nagao's research group (ca. 45% ee).[19] They employed chiral *N*-sulfonyloxaziridine, which was developed by Davis.[20] To improve the optical purity, we tried the reaction of **19** with modified reagents and different counter cations (Table 3).

Both the yields and the ee values were highly dependent on the structure of the reagents and the chosen counter cation of the bis(trimethylsilyl)amide. In the reaction with **20a**,[20a–c] the yield was improved by changing the cation from Li^+ or Na^+ to K^+, but the ee values were unacceptable. Almost no selectivity was observed with **20b**[20d,21a] for all entries. The best result was obtained using the combination of **20c**[20c,e,21] and KHMDS; (*S*)-**21** was obtained in 72% ee and 83% chemical yield.[22] Interestingly, the ee was reduced by changes in the size of the acetal moiety

Table 3 Asymmetric Hydroxylation Reaction of **19** Utilizing Chiral *N*-Sulfonyloxaziridines



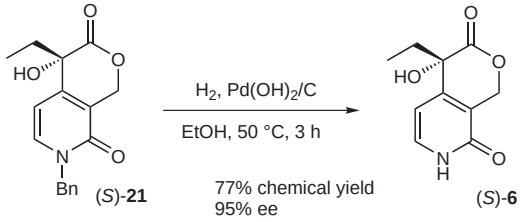
Entry	Base	(*S*)-**21** (%)	Chiral *N*-sulfonyloxaziridine				
			20a (X = H)	**20b** (X = Br)	**20c** (X = MeO)	**20d** (X = EtO)	**20e** (X = OCH_2CH_2O)
1	LiHMDS	Yield	30	98	52	–	–
		ee[a]	23	19	38	–	–
2	NaHMDS	Yield	19	66	5	–	–
		ee[a]	28	25	39	–	–
3	KHMDS	Yield	84	65	**83**	73	54
		ee[a]	29	2	**72**	52	20

[a] The ee was determined by chiral HPLC (Daicel, Chiralcel OD-H, *i*-PrOH–hexane, 1:6).

(**20c**: X = MeO, 72% ee vs **20d**:[21] X = EtO, 52% ee), and the rigid acetal group caused a serious depression of ee (**20e**:[21] X = OCH_2CH_2O, 20% ee). These results suggested that chelation between the oxygen atom in the substrate and the reagent (acetal and oxaziridine) is essential for the high selectivity. Presumably the methyl group in the acetal moiety is the optimum size, when the reagent and the substrate form the complex by chelation. Groups that are bigger or rigid might prevent proper complexation.

Finally, (*S*)-**21** was recrystallized from benzene (91% ee and 66% yield from **19**), and the benzyl group was removed by standard hydrogenolysis conditions to complete the synthesis of the DE ring system of (20*S*)-camptothecin (*S*)-**6**. All the spectral data were identical to those reported[17] and the specific rotation after recrystallization {$[\alpha]_D^{18}$+131.1 (*c* 0.2, $CHCl_3$–MeOH, 4:1), 95% ee[23]} was reasonable in comparison with the previously reported data {Lit.[16] $[\alpha]_D^{23}$ +117.0° (*c* 0.3, $CHCl_3$–MeOH, 4:1), 93% ee; Scheme 3}.

In conclusion, we have demonstrated the straightforward synthesis of the DE ring system of (20*S*)-camptothecin from cheap and commercially available nicotinic acid in six steps. The clarification of the reaction mechanism, especially with regard to diastereoselectivity, is underway in our laboratory.



Scheme 3 Synthesis of the DE ring system of (20*S*)-camptothecin (*S*)-**6**.

References and Notes

(1) (a) Kumar, R.; Chandra, R. In *Advances in Heterocyclic Chemistry*, Vol. 78; Katritzky, A. R., Ed.; Academic Press: San Diego, **2001**, 269. (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(2) Comins, D. L.; Joseph, S. P. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 37.

(3) (a) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5219. (b) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227; and references cited therein.

(4) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111.

(5) (a) Posner, G. H.; Switzer, C. *J. Org. Chem.* **1987**, *52*, 1642. (b) Posner, G. H.; Vinader, V.; Afarinkia, K. *J. Org. Chem.* **1992**, *57*, 4088. (c) Afarinkia, K.; Mahmood, F. *Tetrahedron Lett.* **1998**, *39*, 493; and references cited therein.

(6) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **1999**, *1*, 1031.

(7) (a) Hiroya, K.; Jouka, R.; Kameda, M.; Yasuhara, A.; Sakamoto, T. *Tetrahedron* **2001**, *57*, 9697. (b) Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* **2004**, *6*, 2953. (c) Inamoto, K.; Katsuno, M.; Yoshino, T.; Suzuki, I.; Hiroya, K.; Sakamoto, T. *Chem. Lett.* **2004**, *33*, 1026. (d) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958. (e) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Kida, H.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 12330. (f) Inamoto, K.; Yamamoto, A.; Ohsawa, K.; Hiroya, K.; Sakamoto, T. *Chem. Pharm. Bull.* **2005**, *53*, 1502.

(8) Hiroya, K.; Jouka, R.; Katoh, O.; Sakuma, T.; Anzai, M.; Sakamoto, T. *Arkivoc* **2003**, *(viii)*, 232.

(9) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.

(10) Camptothecin had been isolated from other sources, see: (a) Das, B.; Madhusudhan, P.; Reddy, P. V.; Anitha, Y. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2001**, *40*, 453. (b) Kitajima, M.; Yoshida, S.; Yamagata, K.; Nakamura, M.; Takayama, H.; Saito, K.; Seki, H.; Aimi, N. *Tetrahedron* **2002**, *58*, 9169. (c) Puri, S. C.; Verma, V.; Amna, T.; Qazi, G. N.; Spiteller, M. *J. Nat. Prod.* **2005**, *68*, 1717.

(11) Stork, G.; Schultz, A. G. *J. Am. Chem. Soc.* **1971**, *93*, 4074.

(12) Corey, E. J.; Crouse, D. N.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.

(13) Hsiang, Y.-H.; Hertzberg, R.; Hecht, S.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873.

(14) For reviews on the synthesis of camptothecin and its analogues, see: (a) Du, W. *Tetrahedron* **2003**, *59*, 8649. (b) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585.

(15) For the synthesis of camptothecin since the publications of ref. 14, see: (a) Twin, H.; Batey, R. A. *Org. Lett.* **2004**, *6*, 4913. (b) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879. (c) Yu, J. R.; DePue, J.; Kronenthal, D. *Tetrahedron Lett.* **2004**, *45*, 7247. (d) Chavan, S. P.; Venkatraman, M. S. *Arkivoc* **2005**, *(iii)*, 165. (e) Anderson, R. J.; Raolji, G. B.; Kanazawa, A.; Greene, A. E. *Org. Lett.* **2005**, *7*, 2989.

(16) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255.

(17) Peters, R.; Althaus, M.; Nagy, A.-L. *Org. Biomol. Chem.* **2006**, *4*, 498.

(18) Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4596.

(19) Tagami, K.; Nakazawa, N.; Sano, S.; Nagao, Y. *Heterocycles* **2000**, *53*, 771.

(20) (a) Towson, J. C.; Weismiller, M. C.; Lal, G. S.; Sheppard, A. C.; Kumar, A.; Davis, F. A. *Org. Synth.* **1990**, *69*, 158. (b) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715. (c) Davis, F. A.; Kumar, A.; Chen, B.-C. *Tetrahedron Lett.* **1991**, *32*, 867. (d) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274. (e) Chen, B.-C.; Murphy, C. K.; Kumar, A.; Reddy, R. T.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth.* **1996**, *73*, 159.

(21) (a) Verfürth, U.; Herrmann, R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2919. (b) Page, P. C. B.; Heer, J. P.; Bethell, D.; Lund, A.; Collington, E. W.; Andrews, D. M. *J. Org. Chem.* **1997**, *62*, 6093.

(22) **Asymmetric Hydroxylation of 19 by 20c** (Table 3, entry 3): KHMDS (0.79 mL, 0.59 mmol, 0.75 M solution in toluene) was slowly added to a solution of **19** (152 mg, 0.536 mmol) in anhyd THF (6.0 mL) at –78 °C. After stirring for 30 min, a solution of **20c** (240 mg, 0.829 mmol) in anhyd THF (6.0 mL) was slowly added to the reaction mixture at –78 °C and stirred for 5 h at the same temperature. A sat. aq solution of NH_4Cl and THF were added successively to the mixture and the dry ice–acetone bath was removed. H_2O was added to the mixture and the aqueous phase was extracted with EtOAc. The combined organic solution was washed

with a sat. aq solution of Na_2SO_3 and brine, dried over anhyd $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography [EtOAc–hexane (2:3)] to afford (*S*)-**21** (133 mg, 83%, 72% ee) as a white solid; mp 140 °C (benzene); $[\alpha]_D^{23}$ +107.2 (*c* 1.01, $CHCl_3$, 91% ee). IR (film): 3362, 1747, 1651, 1593, 1564, 1229, 1139, 1047, 880, 748, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (3 H, t, *J* = 7.2 Hz), 1.71–1.87 (2 H, m), 3.65 (1 H, s), 5.11 (1 H, d, *J* = 14.4 Hz), 5.18 (2 H, m), 5.61 (1 H, d, *J* = 16.0 Hz), 6.50 (1 H, d, *J* = 7.2 Hz), 7.20–7.45 (6 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.7, 31.6, 52.3, 66.6, 72.1, 102.9, 119.0, 128.2, 128.3, 128.9, 135.5, 137.4, 148.3, 158.6, 173.7. MS: *m*/*z* (%) = 299 (M^+, 88.8), 270 (20.6), 164 (17.8), 91 (100.0). HRMS: *m*/*z* calcd for $C_{17}H_{17}NO_4$: 299.1157; found: 299.1138. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.07; H, 5.79; N, 4.59.

(23) The ee was determined by chiral HPLC (Daicel, Chiralcel OD-H, EtOH–hexane, 1:9).