New Route to Natural Camptothecin through Isomünchnone Cycloaddition

Alice Kanazawa,* Mauro N. Muniz, Barbora Baumlová, Natalie Ljungdahl, Andrew E. Greene

Département de Chimie Moléculaire (SERCO), UMR 5250, ICMG FR 2650, CNRS Université Joseph Fourier, BP 53, 38041 Grenoble, France
Fax +33(4)76635754; E-mail: Alice.Kanazawa@ujf-grenoble.fr

Received 23 May 2008

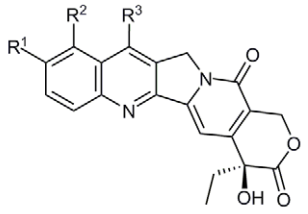
Abstract: A novel approach to camptothecin by [3+2] cycloaddition of an isomünchnone intermediate is described.

Key words: camptothecin, antitumor natural product, isomünchnone cycloaddition, Suzuki coupling, cyanosilylation

Camptothecin (**1**; Figure 1) was first isolated in 1966 by Wall et al. from extracts of *Camptotheca acuminata* ('Xi Shu'or tree of joy), a plant native to China, and found to possess strong antitumor activity.[1] The biological activity of this pentacyclic alkaloid was subsequently attributed to a unique mechanism, the selective poisoning of DNA topoisomerase I, which is an enzyme essential for the relaxation of DNA during important cellular processes.[2]

Several structure–activity studies have been performed since the isolation of this natural product and a number of more active and less severely toxic camptothecinoids have been identified. These research efforts, focused primarily on the synthesis of derivatives bearing substituents on the A and B rings, have led to the discovery of irinotecan [Camptosar (**2**)] and topotecan [Hycamtin (**3**)], which are used for the treatment of ovarian and colon cancers, respectively.[3,4] Several others analogues are in different phases of clinical evaluation.[5,6]

Numerous syntheses of camptothecin and its derivatives have been reported in the literature.[6e,j,7] However, due to the pharmacological importance of the camptothecinoids and their challenging structural features, new synthetic approaches remain of considerable interest. As part of a program to explore new approaches toward camptothecin and its analogues,[8] a novel, enantioselective route to this

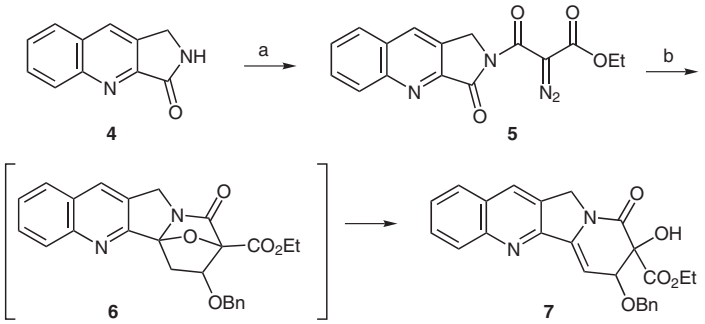


1 $R^1 = R^2 = R^3 = H$ (camptothecin)
2 $R^1 = OCOPipPip$, $R^2 = H$, $R^3 = Et$ (irinotecan)
3 $R^1 = OH$, $R^2 = CH_2NMe_2 \cdot HCl$, $R^3 = H$ (topotecan)

Figure 1 Camptothecin and analogues [PipPip = 4-(1-piperidino)-1-piperidino]

alkaloid through an isomünchnone [3+2] cycloaddition has been developed and is described herein.

We envisaged that a diazoester could be obtained from the easily accessible tricyclic lactam **4**[9] and used to generate the corresponding isomünchnone intermediate; this, in turn, could undergo a [3+2] cycloaddition[10] with an appropriate olefin to produce an adduct with suitable functionality for constructing the D and E rings of the natural product (Scheme 1). Acylation of lactam **4** with ethyl 2-diazomalonyl chloride[11] did indeed provide, after formation of the corresponding lithium amide with LHMDS in THF, the desired diazoester **5**[12] in 68% yield. Subsequent exposure of the diazoester to excess benzyl vinyl ether[13] in the presence of a catalytic amount of rhodium acetate dimer in refluxing benzene cleanly produced the desired tetracycle **7**[14] in excellent yield. As expected, an efficient [3+2]-cycloaddition reaction had occurred to give the bridged ether **6**, which then suffered ring opening to gen-

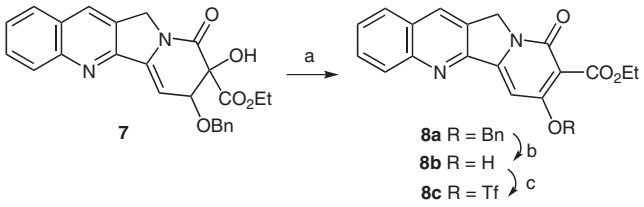


Scheme 1 *Reagents and conditions*: (a) LHMDS, THF, then ethyl diazomalonyl chloride (68%); (b) $[Rh(OAc)_2]_2$, benzyl vinyl ether, benzene (91%).

SYNLETT 2008, No. 15, pp 2275–2278
Advanced online publication: 21.08.2008
DOI: 10.1055/s-2008-1078205; Art ID: G17008ST

erate **7**. This step, however, was not spontaneous and was therefore followed by ^{1}H NMR to ensure complete conversion (91% yield).

In the presence of DBU, tetracycle **7** underwent smooth dehydration to afford pyridone **8a**[15] in high yield (Scheme 2). Having thus rapidly and efficiently completed the A–D rings of camptothecin, the next and final goal was to elaborate the lactone. To this end, pyridone **8a** was debenzylated in the usual way and the derived hydroxy pyridone **8b**[16] was then transformed, also conventionally, into triflate **8c**[17] (84%, 2 steps).

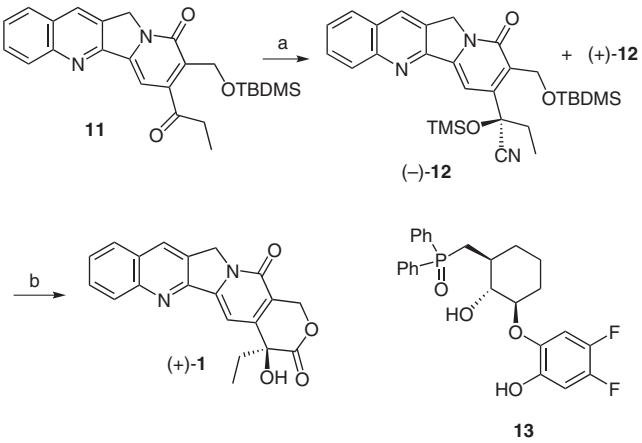


Scheme 2 *Reagents and conditions*: (a) DBU, CH_2Cl_2 (94%); (b) H_2, Pd/C, EtOH (88%); (c) Tf_2O, pyridine, $CHCl_3$ (96%).

With this triflate in hand, a study was effected to evaluate palladium-mediated coupling reactions for introducing a vinylic substituent. While different Stille and Heck reactions proved ineffectual, Suzuki coupling with phenylvinylboronic acid in the presence of tetrakis(triphenylphosphine)palladium and sodium carbonate proceeded smoothly to furnish the styrene derivative **9**[18] in 89% yield (Scheme 3). The ethoxycarbonyl group in **9** was next selectively reduced to produce the corresponding hydroxymethyl derivative **10a**,[19] which was protected as the *tert*-butyldimethylsilyl ether.[20] Oxidative cleavage of the styryl group then readily produced aldehyde **10c**,[21] which was efficiently transformed into ethyl ketone **11**[22] simply by treatment with diazoethane.[23] The crude material was used directly in the next step.

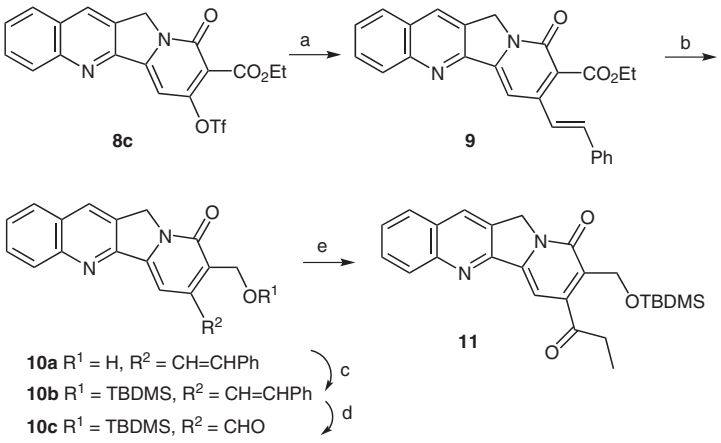
Introduction of the 20*S* stereocenter was addressed through application of Shibasaki's methodology.[24] Thus, ketone **11** was submitted to *S*-enantioselective cyanosilylation with TMSCN in the presence of the Gd complex generated from glucose-derived **13**, which gave a 2:1 mixture of (–)-**12**[25] and (+)-**12** in 66% yield (Scheme 4).[26] Separation of the mixture by chiral HPLC efficiently provided the enantiomers in high purity (≥ 99.8% ee).[27] Since it was found that the undesired minor enantiomer (+)-**12** was converted back into ketone **11** in excellent yield on careful treatment with one equivalent of TBAF in THF at –80 °C, ketone **11** could be, at least in theory, completely transformed into the desired enantiomer (–)-**12**.

The major enantiomer (–)-**12** was successfully converted into natural camptothecin by an intramolecular Pinner reaction on treatment with HCl in hot ethanol (92%). The synthetically derived material {$[\alpha]_D^{20}$ +40.7 (*c* 0.27, $CHCl_3$–MeOH, 4:1); mp 257–258 °C (dec.)} was spectroscopically and chromatographically identical with an authentic sample of (20*S*)-camptothecin.[28]



Scheme 4 *Reagents and conditions*: (a) Gd(O*i*-Pr)$_3$ (10 mol%), **13** (20 mol%), TMSCN (3 equiv), CH_2Cl_2, –20 °C, 60 h (66% from **10c**); (b) chiral HPLC separation, then for (–)-**12** [→ (+)-**1**]: 2 M HCl in Et_2O, EtOH (92%); for (+)-**12** (→ **11**): TBAF (1 equiv), THF, –80 °C (92%).

In summary, a new synthesis of natural camptothecin from a readily available starting material has been developed that employs a [3+2] cycloaddition, a Suzuki coupling, and a Shibasaki enantioselective cyanosilylation as



Scheme 3 *Reagents and conditions*: (a) PhCH=CHB(OH)$_2$, Pd(PPh$_3$)$_4$, aq Na_2CO_3, toluene (89%); (b) DIBAL-H, CH_2Cl_2, then $NaBH_4$, MeOH; (c) TBDMSCl, imidazole, DMF (89%); (d) OsO_4 (cat.), $NaIO_4$, *t*-BuOH, THF–H_2O (99%); (e) $MeCHN_2$, Et_2O–$CHCl_3$.

the key transformations. The synthesis requires 12 steps and proceeds in an overall yield of >15%.

Acknowledgment

We would like to express special gratitude to Prof. M. Shibasaki and Dr. M. Kanai (University of Tokyo) for kindly providing Gd(O*i*-Pr)$_3$ and the ligand **13** and to Prof. C. Roussel and Dr. N. Vanthuyne (Université Paul Cézanne-Marseille) for the enantiomeric separation of enriched **12**. We also thank Prof. P. Dumy (UJF) for his interest in our work, the Swedish Foundation for Strategic Research and Chalmers University of Technology for a study grant (to N.L.), and the Université Joseph Fourier and the CNRS for financial support.

References and Notes

(1) 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.

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

(3) Saltz, L. B.; Cox, J. V.; Blanke, C.; Rosen, L. S.; Fehrenbacher, L.; Moore, M. J.; Maroun, J. A.; Ackland, S. P.; Locker, P. K.; Pirotta, N.; Elfring, G. L.; Miller, L. L. *N. Engl. J. Med.* **2000**, *343*, 905.

(4) Gore, M.; ten Bokkel Huinink, W.; Carmichael, J.; Gordon, A.; Davidson, N.; Coleman, R.; Spaczynski, M.; Heron, J. F.; Bolis, G.; Malmstrom, H.; Malfetano, J.; Scarabelli, C.; Vennin, P.; Ross, G.; Fields, S. Z. *J. Clin. Oncol.* **2001**, *19*, 1893.

(5) (a) Butler, M. S. *Nat. Prod. Rep.* **2008**, *25*, 475. (b) Butler, M. S. *Nat. Prod. Rep.* **2005**, *22*, 162. (c) Cragg, G. M.; Newman, D. J. *J. Nat. Prod.* **2004**, *67*, 332.

(6) For reviews on camptothecin and its derivatives, see: (a) Cuendet, M.; Pezzuto, J. M. In *Modern Alkaloids: Structure, Isolation, Synthesis and Biology*; Fattorusso, E.; Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, **2008**, Chap. 2, 29–33. (b) Lorence, A.; Nessler, C. I. *Phytochemistry* **2004**, *65*, 2735. (c) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585. (d) Pizzolato, J. F.; Saltz, L. B. *Lancet* **2003**, *361*, 2235. (e) Du, W. *Tetrahedron* **2003**, *59*, 8649. (f) Lansiaux, A.; Bailly, C. *Bull. Cancer* **2003**, *90*, 239. (g) Torck, M.; Pinkas, M. *J. Pharm. Belg.* **1996**, *51*, 200. (h) *Camptothecins: New Anticancer Agents*; Potmesil, M.; Pinedo, H., Eds.; CRC Press: Boca Raton, **1995**. (i) Sawada, S.; Yokokura, T.; Miyasaka, T. *Curr. Pharm. Des.* **1995**, *1*, 113. (j) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047.

(7) For recent syntheses of (20*S*)-camptothecin, see: (a) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *Org. Lett.* **2007**, *9*, 2003. (b) Chavan, S. P.; Pathak, A. B.; Kalkote, U. R. *Synlett* **2007**, 2635. (c) Peters, R.; Althaus, M.; Nagy, A.-L. *Org. Biomol. Chem.* **2006**, *4*, 498. (d) Chavan, S. P.; Venkatraman, M. S. *ARKIVOC* **2005**, *(iii)*, 165.

(8) (a) Raolji, G. B.; Garçon, S.; Greene, A. E.; Kanazawa, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 5059. (b) Anderson, R. J.; Raolji, G. B.; Kanazawa, A.; Greene, A. E. *Org. Lett.* **2005**, *7*, 2989. (c) Babjak, M.; Kanazawa, A.; Andersen, R. J.; Greene, A. E. *Org. Biomol. Chem.* **2006**, *4*, 407. (d) Tang, C.-J.; Babjak, M.; Anderson, R. J.; Greene, A. E.; Kanazawa, A. *Org. Biomol. Chem.* **2006**, *4*, 3557.

(9) (a) Danishefsky, S.; Bryson, T. A.; Puthenpurayil, J. *J. Org. Chem.* **1975**, *40*, 796. (b) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **1998**, *120*, 1218.

(10) For reviews on isomünchnone cycloadditions, see: (a) McMills, M. C.; Wright, D. In *The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; John Wiley and Sons: New York, **2002**, 253–314. (b) Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477. (c) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121. (d) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (e) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123.

(11) (a) Marino, J. P.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849. (b) For the use of this reagent for similar cyclizations, see: Padwa, A.; Prein, M. *J. Org. Chem.* **1997**, *62*, 6842.

(12) Compound **5**: mp 215–216 °C (dec.). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 1.29 (t, *J* = 7.1 Hz, 3 H), 4.31 (q, *J* = 7.1 Hz, 2 H), 5.08 (s, 2 H), 7.69 (pseudo t, *J* = 7.5 Hz, 1 H), 7.82 (pseudo t, *J* = 7.2 Hz, 1 H), 7.93 (d, *J* = 7.9 Hz, 1 H), 8.36 (d, *J* = 7.2 Hz, 2 H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 14.6, 46.8, 62.5, 71.0, 128.6, 129.6, 130.0, 130.9, 131.2, 131.4, 132.2, 149.4, 150.1, 161.0, 161.5, 165.0. IR: 2142, 1736, 1717, 1655 cm^{-1}. MS: *m*/*z* = 325 [M + H$^+$]. HRMS: *m*/*z* [M + H$^+$] calcd for $C_{16}H_{13}N_4O_4$: 325.0937; found: 325.0952.

(13) Guy, R. K.; DiPietro, R. A. *Synth. Commun.* **1992**, *22*, 687.

(14) Compound **7**: mp 169–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.1 Hz, 3 H), 4.17–4.29 (m, 3 H), 4.81–4.94 (m, 3 H), 5.01 (s, 2 H), 6.30 (d, *J* = 2.7 Hz, 1 H), 7.25–7.40 (m, 5 H), 7.58 (pseudo t, *J* = 8.0 Hz, 1 H), 7.75 (pseudo t, *J* = 8.5 Hz, 1 H), 7.83 (d, *J* = 8.2 Hz, 1 H), 8.12–8.14 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 48.4, 62.8, 73.1, 80.5, 81.1, 101.7, 127.5, 127.9, 128.0 (2 ×), 128.2, 128.5, 128.6, 129.7, 130.3, 130.8, 137.1, 137.9, 149.0, 152.4, 166.6, 168.6. IR: 3428, 1744, 1659 cm^{-1}. MS: *m*/*z* = 431 [M + H$^+$]. Anal. Calcd for $C_{25}H_{22}N_2O_5$: C, 69.76; H, 5.16; N, 6.51. Found: C, 69.48; H, 5.04; N, 6.41.

(15) Compound **8a**: mp 201–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 5.22 (s, 2 H), 5.35 (s, 2 H), 7.17 (s, 1 H), 7.30–7.50 (m, 5 H), 7.66 (pseudo t, *J* = 7.6 Hz, 1 H), 7.82 (pseudo t, *J* = 8.3 Hz, 1 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 8.32 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 49.2, 61.4, 71.1, 89.6, 109.6, 127.1, 128.1, 128.2, 128.31, 128.34, 128.7, 129.2, 129.6, 130.6, 131.2, 135.3, 147.8, 148.7, 152.0, 159.0, 164.9, 166.2. IR: 1718, 1651, 1602 cm^{-1}. MS: *m*/*z* = 413 [M + H$^+$]. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.81; H, 4.89; N, 6.80. Found: C, 72.70; H, 4.84; N, 6.59.

(16) (a) Compound **8b**: mp 246–248 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.0 Hz, 3 H), 4.50 (q, *J* = 7.1 Hz, 2 H), 5.23 (s, 2 H), 7.03 (s, 1 H), 7.67 (pseudo t, *J* = 7.3 Hz, 1 H), 7.83 (pseudo t, *J* = 7.2 Hz, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 8.37 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$–MeOH, 4:1): δ = 14.1, 50.0, 61.9, 94.6, 128.0, 128.3, 128.4, 129.2, 129.3, 130.6, 131.4, 148.5, 149.7, 151.3, 155.9, 159.3, 171.5, 175.6. IR: 3447, 1660, 1616 cm^{-1}. MS: *m*/*z* = 323 [M + H$^+$]. Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.70. Found: C, 67.23; H, 4.37; N, 8.71. (b) For an alternative synthesis, see: Liao, T. K.; Nyberg, W. H.; Cheng, C. C. *J. Heterocycl. Chem.* **1971**, *8*, 373.

(17) Compound **8c**: mp 205–207 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, *J* = 7.2 Hz, 3 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 5.28 (s, 2 H), 7.28 (s, 1 H), 7.70 (pseudo t, *J* = 8.1 Hz, 1 H), 7.85 (pseudo t, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 7.7 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 8.41 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 50.8, 62.5, 94.8, 115.7, 116.2, 120.5, 128.1, 128.5, 128.7, 129.5, 131.1, 131.6, 148.7,

149.0, 150.4, 156.9, 158.1, 161.6. IR: 1730, 1654, 1616 cm^{-1}. MS: *m/z* = 455 [M + H^+]. Anal. Calcd for $C_{19}H_{13}F_3N_2O_6S$: C, 50.23; H, 2.89; N, 6.17. Found: C, 50.11; H, 2.99; N, 6.10.

(18) Compound **9**: mp 261–263 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3 H), 4.52 (q, *J* = 7.1 Hz, 2 H), 5.30 (s, 2 H), 7.20–7.70 (m, 9 H), 7.84 (pseudo t, *J* = 7.7 Hz, 1 H), 7.95 (d, *J* = 8.1 Hz, 1 H), 8.26 (d, *J* = 8.4 Hz, 1 H), 8.40 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 49.9, 61.8, 97.1, 122.5, 122.9, 127.4, 127.9, 128.1, 128.2, 128.8, 129.0, 129.3, 129.5, 130.5, 131.0, 135.8, 136.8, 145.7, 147.1, 148.7, 152.4, 158.7, 166.3. IR: 1723, 1640, 1603 cm^{-1}. MS: *m/z* = 409 [M + H^+]. Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.46; H, 4.94; N, 6.86. Found: C, 76.37; H, 4.99; N, 6.67.

(19) Compound **10a**: mp 261–263 °C (dec.). ^1H NMR (300 MHz, DMSO-d_6): δ = 4.74 (d, *J* = 5.1 Hz, 2 H), 4.99 (t, *J* = 5.1 Hz, 1 H), 5.25 (s, 2 H), 7.30–7.50 (m, 3 H), 7.60–7.90 (m, 7 H), 8.10–8.25 (m, 2 H), 8.67 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$–MeOH, 4:1): δ = 49.8, 55.9, 99.4, 122.5, 126.4, 127.1, 127.6, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.9, 130.5, 131.3, 135.8, 136.3, 143.5, 147.4, 148.2, 152.3, 161.9. IR: 3310, 1652, 1580, 1566 cm^{-1}. MS: *m/z* = 367 [M + H^+]. HRMS: *m/z* [M + H^+] calcd for $C_{24}H_{19}N_2O_2$: 367.1447; found: 367.1455.

(20) Compound **10b**: mp 247–248 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.16 (s, 6 H), 0.93 (s, 9 H), 5.02 (s, 2 H), 5.27 (s, 2 H), 7.27–7.47 (m, 5 H), 7.59–7.73 (m, 4 H), 7.82 (pseudo t, *J* = 7.7 Hz, 1 H), 7.92 (d, *J* = 7.4 Hz, 1 H), 8.24 (d, *J* = 8.5 Hz, 1 H), 8.35 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.1, 18.3, 26.0, 49.9, 56.6, 88.4, 98.4, 124.5, 127.2, 127.4, 127.5, 128.0, 128.1, 128.7, 128.8, 129.0, 129.6, 130.3, 130.9, 134.9, 136.6, 143.6, 147.7, 148.6, 153.2, 161.0. IR: 1656, 1651, 1593 cm^{-1}. MS: *m/z* = 481 [M + H^+]. Anal. Calcd for $C_{30}H_{32}N_2O_2Si$: C, 74.87; H, 6.71; N, 5.83. Found: C, 74.87; H, 6.76; N, 5.89.

(21) Compound **10c**: mp 262–265 °C (dec.). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.14 (s, 6 H), 0.90 (s, 9 H), 5.15 (s, 2 H), 5.27 (s, 2 H), 7.63–7.66 (m, 2 H), 7.80 (pseudo t, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 7.90 (d, *J* = 8.1 Hz, 1 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 8.34 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4, 18.3, 25.7, 50.3, 57.2, 97.4, 127.8, 127.9, 128.5, 129.8, 130.4, 130.9, 134.6, 143.5, 145.1, 149.0, 152.6, 160.7, 192.2. IR: 1697, 1651, 1600 cm^{-1}. MS: *m/z* = 407 [M + H^+]. Anal. Calcd for $C_{23}H_{26}N_2O_3Si$: C, 67.95; H, 6.45; N, 6.90. Found: C, 68.12; H, 6.43; N, 6.89.

(22) Compound **11**: mp 200–201 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 6 H), 0.91 (s, 9 H), 1.22 (t, *J* = 7.2 Hz, 3 H), 2.91 (q, *J* = 7.2 Hz, 2 H), 4.91 (s, 2 H), 5.28 (s, 2 H), 7.16 (s, 1 H), 7.65 (pseudo t, *J* = 7.0 Hz, 1 H), 7.81 (pseudo t, *J* = 7.7 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 8.37 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.6, 7.6, 18.6, 25.8, 36.2, 50.3, 58.5, 98.5, 127.7, 127.8, 127.9, 128.0, 128.6, 129.6, 130.4, 130.9, 144.5, 148.7, 150.3, 152.5, 159.9, 205.6. IR: 1708, 1649, 1596 cm^{-1}. MS: *m/z* = 435 [M + H^+]. Anal. Calcd for $C_{25}H_{30}N_2O_3Si$: C, 69.10; H, 6.96; N, 6.45. Found: C, 69.19; H, 7.07; N, 6.55.

(23) Warner, C. R.; Walsh, E. J.; Smith, R. F. *J. Chem. Soc.* **1962**, 1232.

(24) (a) Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908. (b) Yabu, K.; Masumoto, S.; Kanai, M.; Shibasaki, M. *Heterocycles* **2003**, *59*, 369.

(25) Compound (–)-**12**: mp 228–231 °C (dec.); $[\alpha]_D^{22}$ –18 (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.19 (s, 3 H), 0.20 (s, 3 H), 0.28 (s, 9 H), 0.93 (s, 9 H), 1.09 (t, *J* = 7.3 Hz, 3 H), 2.37 (q, *J* = 7.3 Hz, 2 H), 5.05 (ABq, *J* = 10.8 Hz, 1 H), 5.21 (ABq, *J* = 10.8 Hz, 1 H), 5.26 (s, 2 H), 7.58–7.66 (m, 2 H), 7.80 (pseudo t, *J* = 7.7 Hz, 1 H), 7.89 (d, *J* = 8.1 Hz, 1 H), 8.23 (d, *J* = 8.4 Hz, 1 H), 8.34 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.4, –5.3, 1.0, 8.5, 18.5, 25.9, 37.2, 50.2, 56.6, 76.0, 99.1, 120.0, 127.5, 127.7, 128.0, 128.7, 129.8, 130.3, 130.7, 144.4, 148.9, 151.2, 152.7, 161.2. IR: 1652, 1598 cm^{-1}. MS: *m/z* = 534 [M + H^+]. HRMS: *m/z* [M + H^+] calcd for $C_{29}H_{40}N_3O_3Si_2$: 534.2608; found: 534.2616.

(26) Dichloromethane was used as the solvent for this reaction instead of a more usual one (THF or EtCN) because of solubility problems. The reaction was performed at –20 °C for the same reason.

(27) Analytical HPLC of **12** was performed on a Chiralpak® IA column (250 × 4.6 mm) using hexane–*i*-PrOH (9:1) as the eluent with a flow rate of 1.0 mL/min and UV monitoring at λ = 254 nm [t_R (+)-**12** = 10.2 min; t_R (–)-**12** = 7.5 min]. The separation was performed using the same chiral support (250 × 10 mm) and eluent with a flow rate of 5 mL/min.

(28) (20*S*)-Camptothecin was purchased from Sigma-Aldrich.