Tetrahedron Letters 50 (2009) 3306–3310

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Ti(III)-mediated radical cyclization of β-aminoacrylate containing epoxy alcohol moieties: synthesis of highly substituted azacycles ☆

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ARTICLE INFO

Article history:
Received 12 January 2009
Revised 6 February 2009
Accepted 10 February 2009
Available online 13 February 2009

Keywords:
Piperidine
Pyrrolidine
Indolizidine
Ti(III)-mediated epoxide opening
Radical cyclization
β-Aminoacrylates

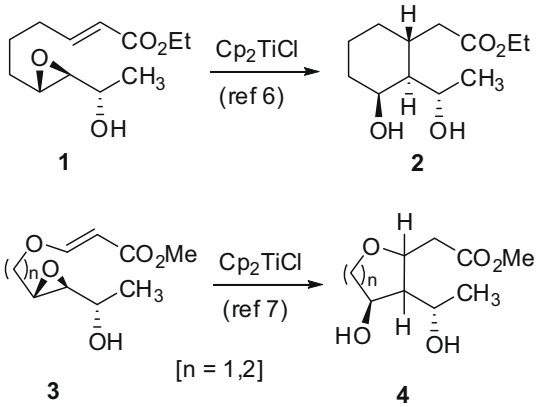
ABSTRACT

Ti(III)-mediated radical cyclization of β-aminoacrylate containing 2,3-epoxy alcohol moieties led to the formation of highly substituted piperidine and pyrrolidine rings. The pyrrolidine ring system was then transformed into an indolizidine framework present in many natural products.

Piperidine, pyrrolidine, and indolizidine/quinolizidine are important structural scaffolds of several natural products.[1] In the literature, radical cyclization of β-alkoxyacrylates and β-aminoacrylates has been extensively used as versatile tools for the construction of oxacyclic[2,3] and azacyclic[4] rings with the latter having applications in the synthesis of many alkaloids. Recently, we have reported that radicals formed during the opening of 2,3-epoxy alcohols **1** and **3** with $Cp_2Ti(III)Cl$[5] could be trapped intramolecularly by a suitably positioned α,β-unsaturated ester moiety in the same molecule giving rise to a cyclohexane ring system **2**,[6] tetrahydrofurans, and tetrahydropyrans **4** (see Scheme 1).[7]

Focusing on our work on the synthesis of carbocycles, oxacycles, and azacycles via Ti(III)-mediated radical cyclization reactions, we wish to report here the cyclization reaction of β-aminoacrylates through epoxide opening followed by 5-exo and 6-exo cyclizations. The details of the process are outlined in Schemes 2–4. Scheme 2 describes the synthesis of a highly substituted piperidine moiety. The synthesis started from the commercially available compound **5**. Tosylation of **5** with tosyl chloride followed by treatment with methyl propiolate in the presence of *N*-methylmorpholine (NMM) gave the 'β-aminoacrylate' intermediate **6**.[8] Cleavage of the acetal **6** with formic acid followed by Wittig olefination with stabilized ylide $Ph_3P{=}CHCOCH_3$ led to an α,β-unsaturated keto compound **7**.

A Luche reduction[9] of **7** followed by a Sharpless kinetic resolution[10] of the resultant racemic allylic alcohol afforded chiral epoxy alcohol **8** >92% ee as determined using the Mosher ester method[11] in 45% yield. With this epoxide in our hand, we turned our attention to carry out the crucial epoxide ring opening reaction followed by cyclization. Accordingly, when epoxy alcohol **8** was treated with $Cp_2Ti(III)Cl$, generated in situ from Cp_2TiCl_2, Zn dust and freshly fused $ZnCl_2$, it underwent epoxide opening at the C-2 position from



Scheme 1.

☆ CDRI Communication No. 7694.

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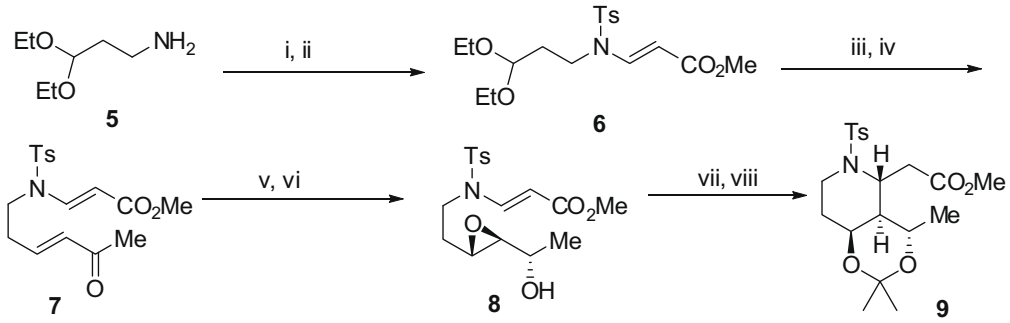
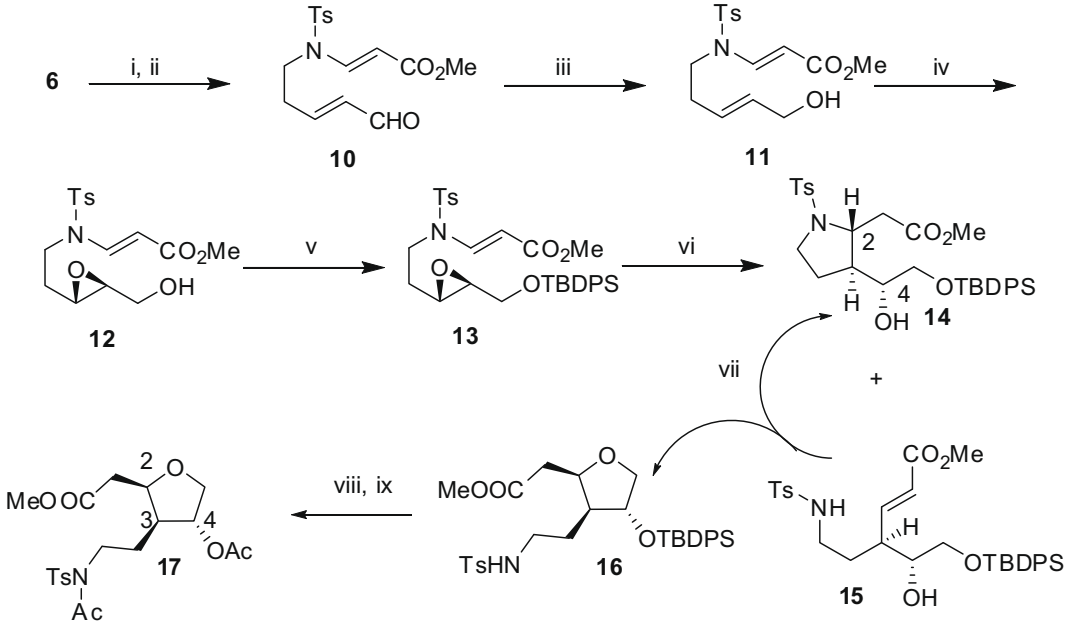
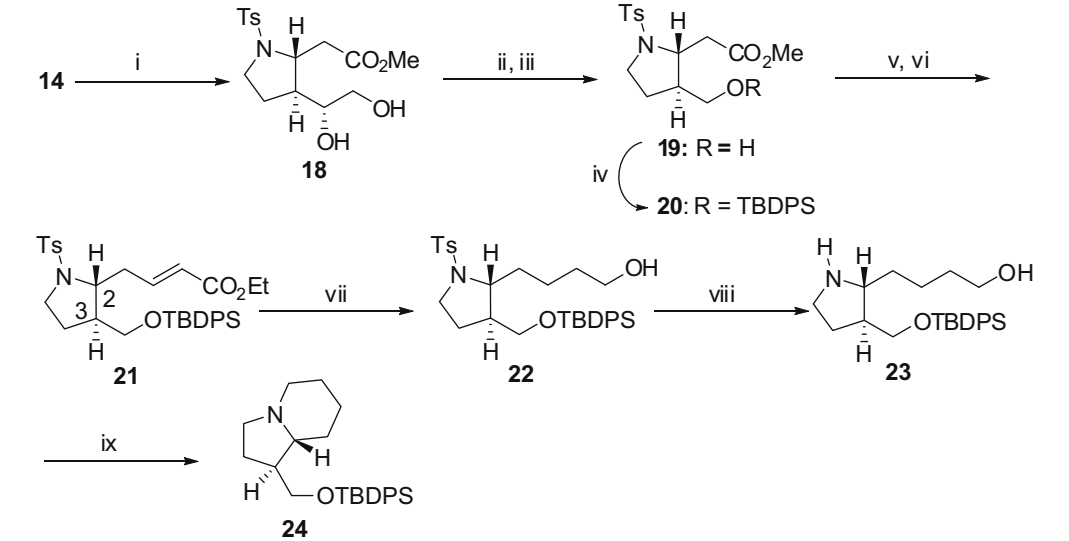
doi:10.1016/j.tetlet.2009.02.063



Scheme 2. Reagents and conditions. (i) TsCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 2 h; (ii) methyl propiolate, NMM, CH_2Cl_2, rt, 1 h, 76% over two steps; (iii) 20% HCO_2H, pentane, 0 °C, 0.5 h; (iv) $Ph_3P{=}CHCOCH_3$, CH_2Cl_2, rt, 8 h, 85% over two steps; (v) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 15 min; (vi) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, MS (4 Å), CH_2Cl_2, −20 °C, 0.5 h, 45% over two steps; (vii) Cp_2TiCl_2, $ZnCl_2$, Zn, THF, −20 °C to rt, 8 h; (viii) 2,2-dimethoxypropane, CSA (cat.), CH_2Cl_2, 2 h, 40% in two steps.



Scheme 3. Reagents and conditions. (i) 20% HCO_2H, pentane, 0 °C, 0.5 h; (ii) $Ph_3P{=}CHCHO$, C_6H_6, reflux, 6 h, 60% in two steps; (iii) $NaBH_4$, $CeCl_3$, MeOH, rt, 24 h, 55%; (iv) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, MS (4 Å), CH_2Cl_2, −20 °C, 2 h, 85%; (v) TBDPSCl, Et_3 N, CH_2Cl_2, DMAP (cat.), 0 °C to rt, 4 h, 95%; (vi) Cp_2TiCl_2, $ZnCl_2$, Zn, THF, −20 °C to rt, 6 h; (vii) **15**, K_2CO_3, MeOH, 0 °C, 2 h, 69% (combined yield) over two steps; (viii) TBAF, THF, 0 °C to rt, 2 h, 85%; (ix) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 0.5 h, 90%.



Scheme 4. Reagents and conditions. (i) TBAF, THF, 0 °C, 1 h; (ii) $NaIO_4$, THF/H_2O (1:1) 0 °C, 15 min; (iii) $NaBH_4$, MeOH, rt, 10 min; (iv) TBDPSCl, Et_3N, CH_2Cl_2, DMAP (cat.), 0 °C to rt, 4 h, 70% over four steps; (v) DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (vi) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 8 h, 80% in two steps; (vii) $LiBH_4$, THF/H_2O (20:1), 0 °C to rt, 24 h, quantitative; (viii) $Na^+C_{10}H_8^-$ DME, −60 °C, 10 min, 85%; (ix) Ph_3P, CBr_4, Et_3 N, CH_2Cl_2, 24 h, 60%.

the hydroxy side[12] and gave a radical intermediate that underwent facile intramolecular trapping by the acrylate moiety leading to the formation of the six-membered piperidine as the only isolable product along with some unidentified complex mixture of compounds. Next, the resulting diol was protected as an acetonide to furnish the bicyclic compound **9** as a white crystalline solid.[13]

The absolute stereochemistry of **9** was established unequivocally from its single-crystal X-ray analysis[14], which confirmed the assigned structure (Fig. 1).

Next, we wanted to test this reaction in a substrate containing primary epoxy alcohol. For this, we started from compound **6** as shown in Scheme 3. Cleavage of the acetal protection with formic acid followed by the Wittig reaction of the resulting aldehyde with $Ph_3P{=}CHCHO$ in refluxing benzene furnished the α,β-unsaturated aldehyde **10** in 60% yield over two steps.

The Luche reduction[9] of **10** provided the allylic alcohol **11,** which was subjected to Sharpless asymmetric epoxidation[10] using L-(+)-DIPT to furnish chiral epoxy alcohol **12**. However, treatment of the primary epoxy alcohol with $Cp_2Ti(III)Cl$ gave only an allylic alcohol[15] and no cyclization product was obtained. The primary hydroxyl group was then protected as a silyl ether and when this epoxide **13** was treated with Ti(III) reagent, it opened the epoxy ring at the C-3 position and the radical at C-3 was trapped intramolecularly by the acrylate moiety furnishing a mixture of the desired cyclized pyrrolidine **14**[16] (minor product, 20%) and a ring opened acyclic product **15** (major one, 70%), which was probably formed by in situ opening of the pyrrolidine **14**. Both **14** and **15** were found to have isomeric products at C3-H in a 4:1 ratio. Compound **15** could, however, be transformed back into the same pyrrolidine **14** in 70% yield on treatment with K_2CO_3 in methanol taking its overall yield to 69%. In this process, we also obtained another highly substituted tetrahydrofuran **16** (~4:1 diastereomeric mixture) in 20% yield from **15**. To know the absolute stereochemistry of **14** (major isomer), we first assigned the stereochemistry of **17**, which was obtained from **16** in two steps. During the course of radical-mediated epoxide opening and subsequent base-catalyzed cyclization, the absolute stereochemistry at C-4 of **14** was retained as *R* as it was in the chiral epoxide **12**. The C-5 protons decoupled ^{1}H NMR spectrum of **17** showed a doublet (J = 1.62 Hz) at 5.03 ppm for C4–H signal indicating that the C3–H and C4–H had a *trans*-relationship and that the absolute stereochemistry of C-3 in **17**, and hence in **14**, was *S*. The absolute stereochemistry of C-2 in **14** was established at a later stage.

Next, we wanted to transform the pyrrolidine moiety to an indolizidine frame work, which is a very important building block for many natural products.[1e–k] For the synthesis of the indolizidine frame work, shown in Scheme 4, we started from **14** which was treated with TBAF to provide diol **18**. Further oxidative cleavage of the resulting diol with $NaIO_4$ gave an aldehyde that was treated with $NaBH_4$ to form primary alcohol **19**. The protection of the primary alcohol of **19** as a TBDPS ether gave **20** as a single isomer after removing the minor isomer via silica gel column chromatography. The treatment of **20** with 1 equiv of DIBAL-H followed by Wittig olefination with stabilized ylide $Ph_3P{=}CHCO_2Et$ gave α,β-unsaturated ester compound **21**[17] as a white crystalline compound. The stereochemistry of **21** was determined by the ^3J values of the C2–H proton. It appeared as a ddd at 3.62 ppm with coupling constants of 7.8, 3.7, and 3.5 Hz. One of the CH_2–CH=CH–CO_2Et protons appeared as a ddd at 2.67 ppm with coupling constants 14.5, 7.4, and 3.7 Hz. The other one appeared as a td at 2.58 ppm with coupling constants 14.5 and 7.8 Hz. So the coupling constant between C2–H and C3–H is 3.5 Hz, which indicates that the relationship between C2–H and C3–H was *trans*. The absolute stereochemistry of **21** was, finally, unequivocally established from the single-crystal X-ray analysis[18] which clearly showed the assigned structure (Fig. 2). Consequently, it also proved that the absolute stereochemistry at C-2 in **14** was *R*.

Next, the reduction of **21** with $LiBH_4$ gave saturated primary alcohol **22**, which on treatment with sodium naphthalenide[19] provided the detosylated product **23**. The transformation of primary alcohol to the corresponding alkyl bromide followed by cyclization[20] gave the desired indolizidine framework **24**. The spectral and analytical data of **24**[21] were in good agreement with those reported in the literature.

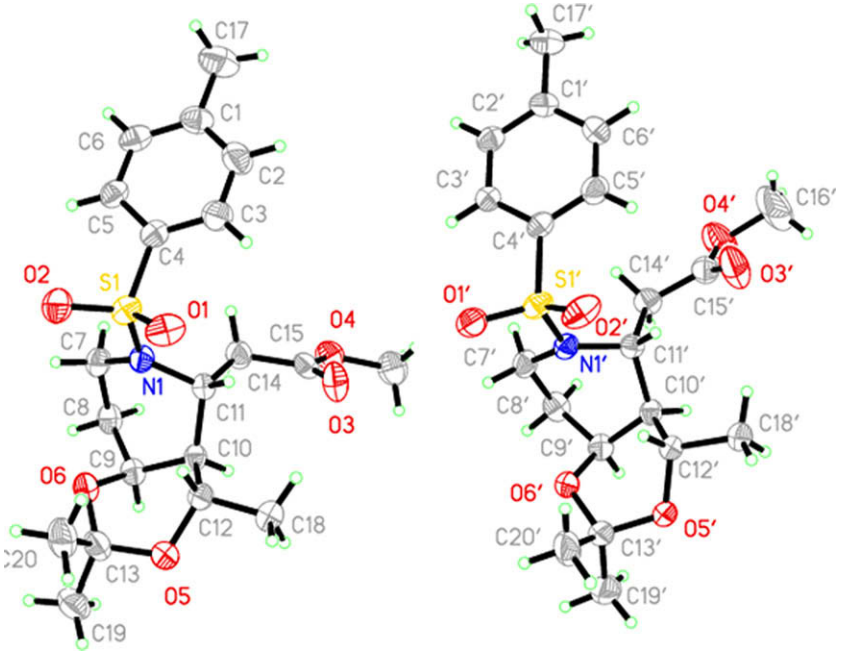


Figure 1. X-ray crystal structure of **9**. Perspective view of the two independent molecules showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level, and H atoms are shown as small spheres of arbitrary radii.

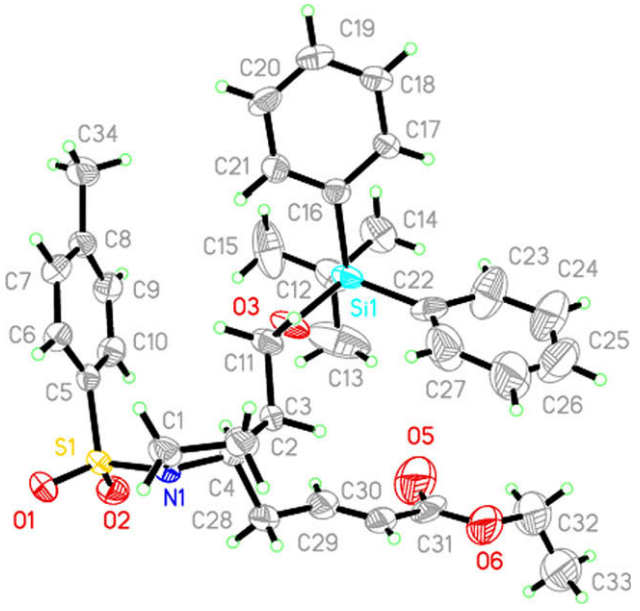


Figure 2. X-ray crystal structure of **21**. Displacement ellipsoids are drawn at 30% probability level, and H atoms are shown as small spheres of arbitrary radii.

In conclusion, we have demonstrated the Ti(III)-mediated radical cyclization of 'β-aminoacrylate' containing 2,3-epoxy alcohols, and this method can be extended to the synthesis of many natural products containing piperidine, pyrrolidine, and indolizidine/quinolizidine moieties.

Acknowledgments

The authors wish to thank DST, New Delhi for the Ramanna Fellowship (SR/S1/RFOC-06/2006; T.K.C.) and CSIR, New Delhi for research fellowships (R.S. and S.R.).

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13. *Analytical and spectral data of compound* **9**: $R_f = 0.4$ (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{31}$ +25.8 (*c* 0.53 in $CHCl_3$); IR (neat): ν_{max} 2985, 2934, 1735, 1332, 1154 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.71 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 4.17–3.98 (m, 2H), 3.65 (s, 3H), 3.58 (m, 1H), 3.37 (m, 1H), 3.18 (td, $J = 11.6$, 5.1 Hz, 1H), 2.54–2.46 (m, 2H), 2.43 (s, 3H), 2.16–1.81 (m, 2H), 1.60 (dd, $J = 9.4$, 6.5 Hz, 1H), 1.24 (s, 3H), 1.15 (d, $J = 6.5$ Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 143.4, 137.0, 129.6, 127.0, 99.3, 64.8, 62.9, 51.8, 48.9, 46.4, 39.8, 37.8, 26.5, 26.4, 24.7, 21.4, 18.9; MS (ESI): *m/z* (%) 412 (15) $[M+H]^+$, 434 (35) $[M+Na]^+$; HRMS (ESI): calcd for $C_{20}H_{29}NO_6NaS$ $[M+Na]^+$ 434.1613, found 434.1609.
14. *X-ray Crystal data for compound* **9**: Crystal data, $C_{20}H_{29}NO_6S$, $M = 411.5$, orthorhombic, space group $P2_12_12_1$, $a = 8.2570(6)$ Å, $b = 18.0755(14)$ Å, $c = 28.902(2)$ Å, $V = 4313.6(5)$ Å^3, $d_{calcd} = 1.267$ Mg m^{-3}. Data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) with ω-scan method.[22] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 9359 reflections for compound **9.** Integration and scaling of intensity data were accomplished using SAINT program.[22] The structure was solved by Direct Methods using SHELXS97[23] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[23] All the hydrogen atoms were positioned geometrically and were treated as riding on their parent carbon atoms, with C–H distance of 0.93–0.98 Å and an O–H = 0.82 Å, with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$(methyl C and O). The structure was refined with $R_1 = 0.0373$, $wR_2 = 0.0972$ for 986 reflections with $I > 2\sigma(I)$. Crystallographic data has been deposited for compound **9** with the Cambridge Crystallographic Data Centre [CCDC No. 696654]. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].
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16. Analytical and spectral data of compound **14** (major isomer): $R_f = 0.6$ (silica gel, 30% EtOAc in hexane); IR (neat): ν_{max} 2932, 1735, 1431, 1341, 1159, 1104 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.77–7.19 (m, 14H), 3.71 (m, 1H); 3.57 (s, 3H), 3.54–3.28 (m, 2H), 3.24–2.99 (m, 3H), 2.93 (dd, $J = 16.1$, 3.6 Hz, 1H), 2.53 (dd, $J = 16.1$, 8.8 Hz, 1H), 2.38 (s, 3H), 2.01 (m, 1H), 1.80–1.63 (m, 2H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 143.5, 135.4, 134.1, 132.7, 129.9, 129.6, 127.8, 127.6, 70.2, 66.2, 58.6, 51.5, 48.0, 46.7, 40.8, 26.7, 24.3, 21.5, 19.1; MS (ESI): *m/z* (%) 596 (45) $[M+H]^+$, 618 (30) $[M+Na]^+$; HRMS (ESI): calcd for $C_{32}H_{41}NO_6NaSiS$ $[M+Na]^+$ 618.2321, found 618.2300.
17. *Analytical and spectral data of compound* **21**: $R_f = 0.5$ (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{31}$ −22.9 (*c* 0.63 in $CHCl_3$);IR (neat): ν_{max} 2937, 2862, 1718, 1344, 1161, 1103 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, $J = 8.2$ Hz, 2H), 7.49–7.38 (m, 6H), 7.36–7.30 (m, 4H), 7.17 (d, $J = 8.2$ Hz, 2H), 6.90 (td, $J = 15.6$, 7.5 Hz, 1H), 5.85 (d, $J = 15.6$ Hz, 1H), 4.16 (q, $J = 6.7$ Hz, 2H), 3.62 (ddd, $J = 7.8$, 3.7, 3.5 Hz, 1H), 3.37 (m, 1H), 3.05 (ddd, $J = 9.7$, 8.2, 7.4 Hz, 1H), 2.93 (d, $J = 7.4$ Hz, 2H), 2.67 (ddd, $J = 14.5$, 7.4, 3.7 Hz, 1H), 2.58 (td, $J = 7.8$, 14.5 Hz, 1H), 2.36 (s, 3H), 2.04 (m, 1H), 1.82 (m, 1H), 1.43 (m, 1H), 1.28 (t, $J = 7$ Hz, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 144.3, 143.4, 135.4, 134.0, 133.1, 129.8, 129.6, 127.7, 127.4, 124.3, 63.4, 60.7, 60.3, 47.5, 45.1, 38.9, 26.7, 25.8, 21.5, 19.0, 14.2; MS (ESI): *m/z* (%) 606 (15) $[M+H]^+$, 623 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{34}H_{43}NO_5NaSiS$ $[M+Na]^+$ 628.2528, found 628.2498.
18. (a) *X-ray Crystal data for compound* **21**: Crystal data, $C_{34}H_{43}NO_5SSi$, $M = 605.84$, monoclinic, space group $P2_1$, $a = 10.2220(7)$ Å, $b = 8.2252(6)$ Å, $c = 19.9503(14)$ Å, $\beta = 97.939(1)°$, $V = 1661.3(2)$ Å^3, $d_{calcd} = 1.211$ Mg m^{-3}. Data were collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) with ω-scan method.[22] Preliminary lattice parameters and orientation matrices were obtained from four sets of frames. Unit cell dimensions were determined from the setting angles of 5835 reflections for

compound **21.** Integration and scaling of intensity data were accomplished using the SAINT program.[22] The structure was solved by Direct Methods using SHELXS97,[23] and refinement was carried out by full-matrix least-squares technique using SHELXL97.[23] The side chain atoms C30/C31/C32/C33/O6 are disordered over two sites with occupancies of 0.711(14) and 0.289(14). The geometries of the disordered atoms were refined with distance constraints. The displacement parameters of the disordered atoms were restrained. All the hydrogen atoms were positioned geometrically and were treated as riding on their parent carbon atoms, with C–H distance of 0.93–0.98 Å and an O–H = 0.82 Å, with U_{iso}(H) = 1.2U_{eq} (C) or 1.5U_{eq} (methyl C and O). The structure was refined with R_1 = 0.0672, wR_2 = 0.1777 for 5199 reflections with $I > 2\sigma(I)$. The structure is shown in Figure 2. The absolute stereochemistry was confirmed by refinement of the absolute structure parameters {Flack parameter = 0.08(13)}. Crystallographic data have been deposited for compound **21** with the Cambridge Crystallographic Data Center [CCDC No. 696653]. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].; (b) Flack, H. D.; Bernardinelli, G. *J. Appl. Crystallogr.* **2000**, *33*, 1143–1148.

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21. *Analytical and spectral data of compound* **24**: R_f = 0.3 (silica gel, 10% MeOH in $CHCl_3$); $[\alpha]_D^{31}$ +31.1 (*c* 0.37 in $CHCl_3$); IR (neat): ν_{max} 2930, 2858, 1464, 1430, 1108 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.74–7.30 (m, 10H), 3.63 (d, *J* = 4.4 Hz, 2H), 3.23–3.04 (m, 2H), 2.30–1.14 (m, 12H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.6, 133.6, 129.6, 127.6, 67.4, 64.5, 53.3, 52.9, 45.1, 29.6, 29.3, 26.8, 24.4, 23.9, 19.2; MS (ESI): *m/z* (%) 394 (100) $[M+H]^+$; HRMS (ESI): calcd for $C_{25}H_{36}NOSi$ $[M+H]^+$ 394.2566, found 394.2549.
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