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An unusual stereochemical outcome of radical cyclization: synthesis of (+)-biotin

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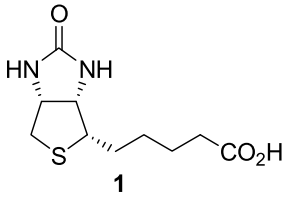
Abstract—An enantioselective synthesis of (+)-biotin **1** starting from naturally available cysteine is described. The key steps are the unusual stereochemical outcome of radical cyclization of compound **10** to prepare 5,5-fused system **11**, and the introduction of C4-sidechain at C_6 in **13** via a Grignard reaction.

1. Introduction

(+)-Biotin **1** is one of the water-soluble B-complex vitamins. In bound from, it is widely distributed as a cell constituent of animal and human tissues.



1

Biochemically, (+)-biotin functions as a cofactor in carboxylation reactions and is also involved in important processes such as gluconeogenesis and fatty acid synthesis.[1] The importance of (+)-biotin in human nutrition and animal health has stimulated the development of new synthetic routes towards this vitamin. To date, a number of new synthetic routes involving different strategies for control of the three adjacent chiral centers have been reported.[2] The formation of five membered rings using radical cyclization has been used extensively in the last few years for the synthesis of complex molecules.[3] From these reports it is evident that the hex-5-enyl radicals predominantly undergo exo cyclization resulting in the formation of 1,5-cis derivatives. Only very few examples are reported where formation of 1,5-trans product is reported.[3b,c,i,j] However, these are restricted to the formation of monocyclic adducts. Although the formation of bicyclic compounds employing radical cyclizations leading to 1,5-trans adducts are known,[3d] they are restricted to the formation of 6,5-fused systems. We are not aware of any instance of acyliminium radical cyclization leading to the formation of 5,5-fused system with 1,5-trans stereochemistry. In our earlier route we have reported an efficient conversion of **10** to a bicyclic 5,5-fused system, utilizing acyliminium ion chemistry[2d] for the synthesis of biotin. Based on literature precedents,[3] it was our premise that radical cyclization of **10** would lead to all cis bicyclic ether **11a**, which is the intermediate having the requisite stereochemistry for the synthesis of biotin. Our continued interest in the synthesis of biotin[2d–f] led us to explore radical cyclization of enol ether **10**. Herein, we describe an interesting approach to the synthesis of (+)-biotin using intramolecular radical cyclization of α-amido radical to the silyl enol ether in **10**. This manuscript delineates our findings towards this end. To the best of our knowledge there is only one report of (+)-biotin synthesis using intramolecular cyclization onto an alkyne.[4]

2. Results and discussion

Our synthetic route to **1** is outlined in the Schemes 1–3. According to the planned synthesis, hydantoin **4** was prepared from L-cysteine hydrochloride hydrate by a literature procedure.[5,6] Reduction of hydantoin **4** with sodium borohydride gave hydroxy imidazothiazolone **5** in

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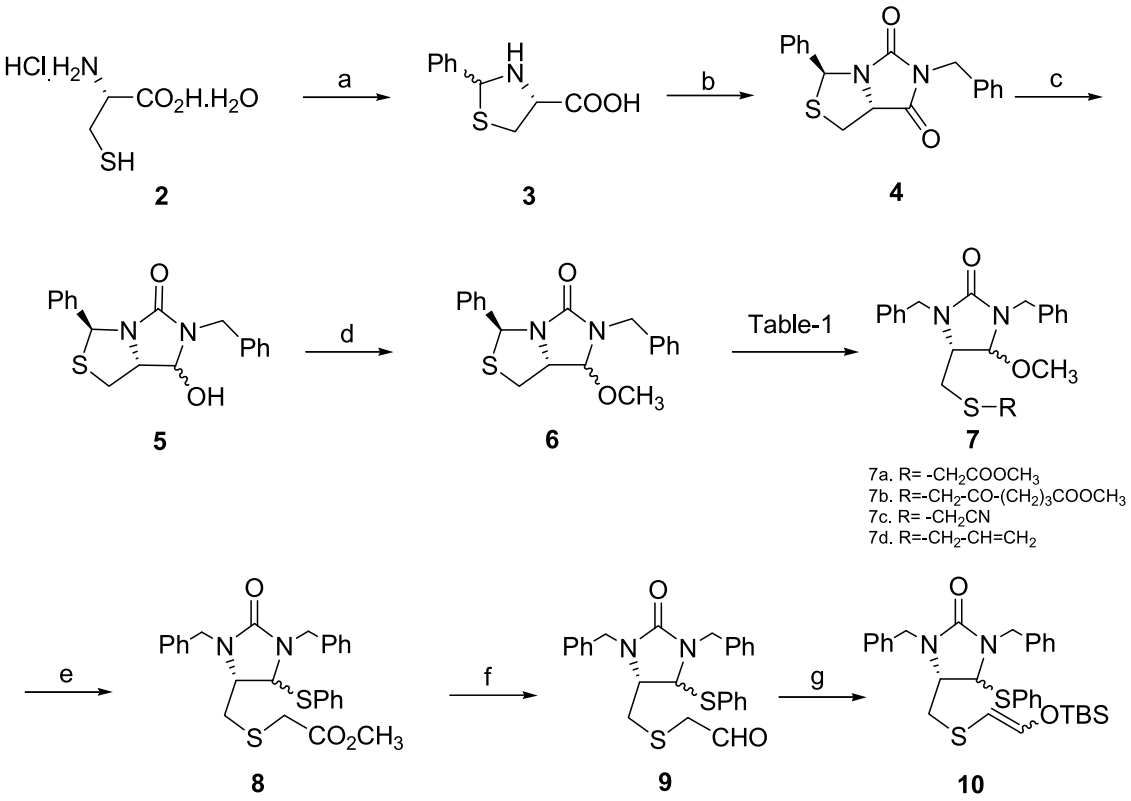
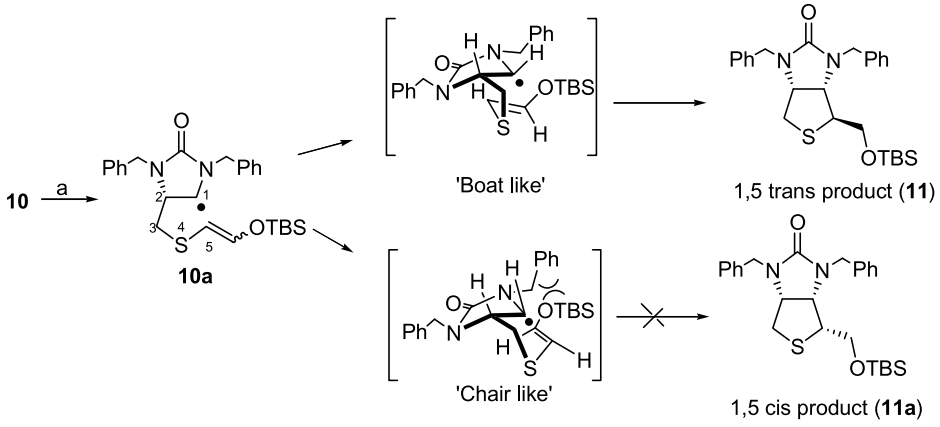


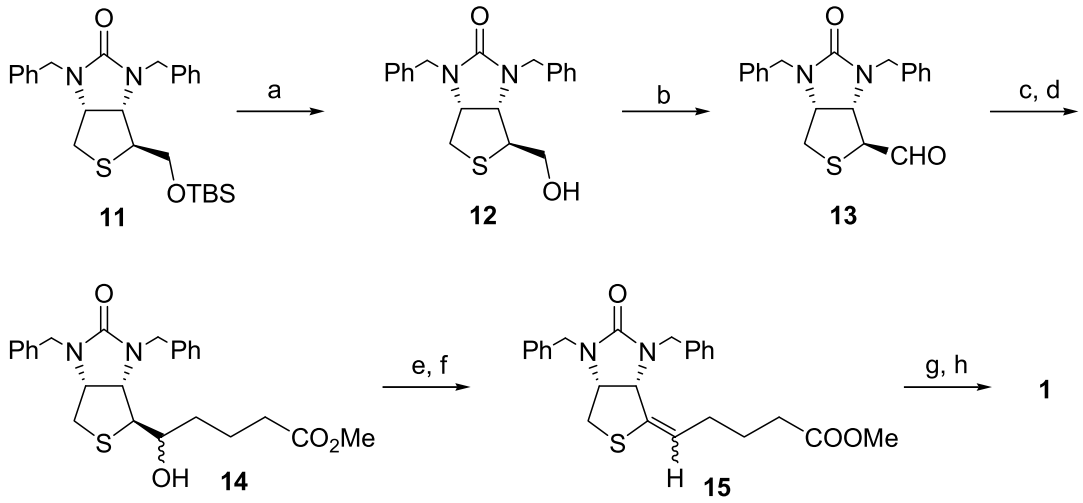
Scheme 1. (a) PhCHO, KOAc, MeOH:H_2O (1:1), rt, 6 h, 98%; (b) BnNCO, DCM, 60 min, concd HCl, 60 min, reflux, 90 min, 90%; (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 99%; (d) MeOH, *p*-TSA (cat.), 15 min, 98%; (e) PhSH, *p*-TSA (cat.), DCM 10 min, 93%; (f) DIBAL-H, toluene, −78 °C, 2 h, 78%; (g) TBSCl, DCM, DBU, reflux, 30 min, 80%.



Scheme 2. (a) Bu_3SnH, AIBN, benzene, reflux, 4 h, 53%.

98% yield, which on methoxylation in the presence of cat. *p*-TSA furnished methoxy imidazothiazolone **6**. Initial attempts to effect reductive cleavage of carbon–sulfur bond under conventional reaction conditions (Zn/AcOH) resulted in exclusive formation of eliminated product by loss of methanol.

It was therefore, necessary to cleave the carbon–sulphur bond of **6** under nonacidic conditions, was achieved by three different methods. Amongst them, compound **6** on reductive cleavage of carbon–sulphur bond with Bu_3SnH in the presence of cat. amounts of AIBN in benzene at elevated temperatures furnished the corresponding tin thiolate, which without isolation was alkylated with ethyl chloroacetate under anhydrous conditions in acetone using K_2CO_3, furnished **7a**. Potassium carbonate was proved necessary for the success of the reaction. Additionally carbon–sulphur bond cleavage was also achieved by using two other methods. viz. (a) Li-naphthalide at −78 °C, (b) Zn/NH_4Cl according to conditions of Houlton.[7] The resulting thiol in both cases without isolation was alkylated under basic conditions with alkyl halides (see Table 1) to furnish the *S*-alkylated compounds (**7a**–**7c**). In order to establish the generality of this protocol, the reductive cleavage of carbon–sulphur bond was studied with a variety of allyl halides. The results of the reductive cleavage followed by



Scheme 3. (a) $BF_3 \cdot Et_2O$, $CHCl_3$, rt, 2 h, 75%; (b) $(COCl)_2$, DMSO, DCM, Et_3N, −78 °C to rt, 2.5 h, 61%; (c) Mg, $BrCH_2CH_2CH_2Br$, THF, 12 h, then cooled to −15 °C, CO_2, 2 h, rt; (d) CH_2N_2, 15 min, 76% (two steps); (e) MsCl, Et_3N, DCM, 0 °C to rt, 3 h; (f) DBU, 60 °C, 12 h, 80% (two steps); (g) 10% Pd–C, H_2, 200 psi, 65 °C, 6 h, 99%; (h) HBr (47%), reflux, 5 h, 75%.

Table 1

	7 (% Yield)			
Alkylating agent	$ClCH_2COOMe$	$ClCH_2C(O)(CH_2)_3COOMe$	$ClCH_2CN$	$ClCH_2CH{=}CH_2$
Method A[a]	**7a** 80%	**7b** 70%	**7c** 78%	**7d** 85%
Method B[b]	**7a** 74%	**7b** 64%	**7c** 76%	**7d** 80%
Method C[c]	**7a** 63%	**7b** 58%	**7c** 70%	**7d** 73%

[a] Reduction of C–S bond with tri-*n*-butyltin hydride.
[b] Reduction of C–S bond with lithium-naphthalide.
[c] Reduction of C–S bond with zinc and saturated aqueous NH_4Cl.

alkylation are tabulated in Table 1. These results clearly establish the superiority of tri-*n*-butyltin hydride as an efficient reagent for reductive cleavage of carbon–sulphur bond as compared to Li-naphthalide or Zn/NH_4Cl.

Compound **7a** was then taken up for the synthesis of biotin. Thus, **7a** was converted to its thiophenyl derivative **8** with excess of thiophenol in dichloromethane and cat. amount of *p*-TSA. The ester moiety in the compound **8** was then reduced to aldehyde **9** with DIBAL-H in toluene at −78 °C, the crude aldehyde **9** was then converted to its TBS enol ether **10** (trans:cis=3:1) by using TBDMSCl, and DBU in dichloromethane at reflux for 30 min. The crucial step of synthesis, the radical cyclisation of silyl enolether **10** according to literature precedents[3] was expected to undergo exo cyclisation leading to 1,5-cis substituted bicyclic skeleton **11a**, which would serve as an ideal precursor for the synthesis of biotin. However, when the silyl enol ether **10** was refluxed with Bu_3SnH and catalytic amount of AIBN under argon atmosphere, a single cyclized product **11** was obtained in 53% yield, which was eventually shown to be the undesired 5,5-fused system **11** with incorrect stereo-center at C-5 position.

The exclusive formation of 1,5-trans product **11** (carbon having radical assigned 1 in hex-5-enyl system **10a**) is unexpected since other structurally related radicals and their carbocyclic analogues[3d] give a mixture with mostly 1,5-cis products. This may be attributed to the manifestation of steric and electronic effects of the acylimido radical. Additionally the presence of electronegative nitrogen may also destabilize the transition state leading to the formation of *syn* product.[3h] We believe that the bulky *N*-benzyl groups of imidazolidinone tend to occupy quasi equatorial positions. The formation of 1,5-trans product **11** can be rationalized by a boat like transition state of **10a** (Scheme 2) in which the pseudo-axial radical attacks the C=C of the enol ether in pseudo-equatorial side chain. By this way the steric compression between *N*-benzyl adjacent to radical carbon and the bulky OTBS group of enol ether could be relieved as compared to the chair like transition state leading to the formation of 1,5-cis product **11a**. This unusual behavior may also be ascribed to the presence of sulfur atom in the chain, which mimics the six membered ring formation.

This reaction shows that 1,5-trans cyclized products could be synthesized by appropriately controlling the steric requirements. More studies are required to arrive at a proper conclusion.

Although the stereochemistry at the C-5 was not the desired one, we decided to proceed further and rectify it at the later stages of the synthesis. In the next step TBS group was deprotected[8] and oxidized to the corresponding aldehyde under Swern oxidative conditions to furnish bicyclic aldehyde **13** with undesired configuration at C-5 position (with respect to (+)-biotin) as the sole product. Since the isomer **13** is thermodynamically more stable, it cannot be epimerized at the C-5 position. The side chain of biotin was

introduced by the addition of excess of 1,3-propane dimagnesium dibromide in THF at −15 °C followed by quenching with CO_2[9] at −20 °C to furnish the carboxylic acid. The carboxylic acid thus formed was characterized as its methyl ester **14** by treating with diazomethane. The hydroxy methyl ester **14** was then converted to (+)-biotin by straight forward functional group manipulations. The hydroxyl function of **14** was protected as its mesylate and subsequent treatment of this with DBU afforded known exocyclic olefin.[10] Hydrogenation of this double bond followed by debenzylation furnished (+)-biotin in 60% yields over four steps.

3. Conclusion

The synthesis of (+)-biotin starting from the commercially available L-cysteine hydrochloride hydrate has been achieved. The noteworthy feature of this synthesis is the unusual stereochemistry observed during the radical cyclization to furnish the cis fused bicyclic system, which highlights the ability of radical cyclizations to form 1,5-trans products of hexenyl radicals by appropriate control of steric requirements.

4. Experimental

4.1. General methods

All solvents were freshly distilled before use and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s, singlet; d, doublet; m, multiplet. Progress of the reactions were monitored by TLC using Merck silica gel. $60F_{254}$ precoated plates and visualized by fluorescence quenching or by charring after treatment with the mixture of *p*-anisaldehyde–H_2SO_4 in ethanol. The products were purified by column chromatography (SiO_2).

Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.

4.1.1. (2*RS*,4*R*)-2-Phenylthiazolidine-4-carboxylic acid (3).[5] To a solution of L-cysteine hydrochloride hydrate **2** (60 g, 0.34 mol), in water (525 mL) was added potassium acetate (36 g, 0.37 mol) was added and allowed to stir till a solution was obtained. To this solution 95% of methanol (525 mL) was added followed by immediate addition of benzaldehyde (44.2 g, 0.42 mol) in one portion. The reaction mixture was kept at 25 °C for 3 h and an additional 3 h at 0 °C. The product was formed as a solid was filtered, washed with methanol, and dried to afford **3** as a white solid. Yield: 72.0 g (98%). Mp 155 °C (lit.[5] 159–160 °C), $[\alpha]_D$ −133 (*c* 1, DMSO) IR (KBr, cm^{-1}): 3040, 2960, 2700–2400 (NH_3^+), 1600–1550 (CO_2^-) 1360. ^{1}H NMR (DMSO-d_6, 200 MHz): 3.50–3.30 (m, 2H, CH_2); 4.40–4.0 (dd, 1H, CHCOOH); 5.80 (s, 1H, CH); 6.80 (bm, 1H, NH); 7.40 (m, 5H). Mass (*m*/*z*): 209 (M^+, 34), 170 (39), 164 (65), 137 (100), 77 (10), 65 (8), 55 (7).

4.1.2. 6-Benzyl-3-phenyl(3*S*,7a*R*)perhydroimidazo[1,5-*c*][1,3]thiazol-5,7-dione (4). In a 500 mL two-necked round bottom flask filled with nitrogen, (20.0 g, 95.6 mmol) thiazolidine carboxylic acid **3** was placed in 150 mL of anhydrous THF. To this suspension, a solution of (15.2 g, 1.143 mol) benzyl isocyanate in 50 mL of THF was added dropwise over a period of 20 min. The reaction mixture was stirred for 1 h at 60 °C. The reaction mixture was then cooled to 0 °C and concd HCl (20.0 mL) was added and the reaction mixture was allowed to stir for 90 min at 60 °C. Then the reaction mixture was allowed to cool to room temperature, water was added and extracted with ethyl acetate (3×200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. After triturating with methanol the hydantoin **4** was obtained as a white crystalline solid 27.8 g, (90%). Mp 78 °C, $[\alpha]_{365}^{20}$ +1010 (*c* 1, $CHCl_3$); $[\alpha]_D$ −250 (*c* 1.08, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050. ^{1}H NMR ($CDCl_3$, 200 MHz): 3.17 (dd, 1H, *J*=7.82, 11.2 Hz); 3.30 (dd, 1H, *J*=6.81, 11.2 Hz); 4.52 (t, 1H, *J*=7.32 Hz); 4.68 (s, 2H); 6.43 (s, 1H); 7.39 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 33.2 (t), 42.81 (t), 65.19 (d), 65.82 (d), 126.36 (d), 127.41 (d), 127.91 (d), 128.05 (d), 125.15 (d), 128.28 (d), 128.42 (d), 128.48 (d), 128.72 (d), 128.80 (d), 135.44 (s), 139.04 (s), 158.54 (s, C=O), 171.0 (s, C=O). Mass (*m*/*z*): 325 (M+1, 30), 324 (M^+, 100), 323 (M−1, 40), 291 (9), 278 (4), 233 (28), 162 (22), 145 (5), 132 (8), 122 (14), 117 (39), 104 (9), 91 (38), 77 (10), 65 (8), 55 (7). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.38; H, 5.17; N, 8.43; S, 9.65.

4.1.3. (3*S*,7a*R*)-6-Benzyl-7-hydroxy-3-phenyltetrahydro-5*H*-imidazo[1,5-*c*][1,3]thiazol-5-one (5). The imidazolidinone **4** (32.4 g, 0.1 mmol) was taken in aqueous THF or methanol (300 mL) and cooled to 0 °C. Sodium borohydride (5.6 g, 0.15 mol) was added gradually in small portions over a period of time (30 min). After addition of sodium borohydride was complete, the reaction mixture was brought to room temperature and stirring continued for additional half an hour. The reaction mixture was then quenched with water and the contents were extracted with ethyl acetate. The combined layers were washed with water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4 and filtered. After concentration under reduced pressure a white crystalline solid of hydroxy imidazothiazolone **5**, which was sufficiently pure. Yield: 32.5 g (99%). Mp 113 °C, $[\alpha]_D$ +52.58 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3400, 3010, 2960, 1700, 1510, 1438, 1310, 1239, 1160, 959. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.92 (dd, 1H, *J*=6.83, 11.72 Hz); 3.23 (d, 1H, *J*=10.26 Hz, –O*H*, D_2O exchangeable); 3.33 (dd, 1H, *J*=5.37, 11.72 Hz); 4.18 (d, 1H, *J*=15.14 Hz); 4.19 (m, 1H, *J*=5.37, 6.83 Hz, –C*H*–CH–OH); 4.78 (d, 1H, *J*=15.14 Hz); 5.04 (dd, 1H, *J*=6.84, 10.26 Hz, N–C*H*–OH); 6.38 (s, 1H); 7.30 (m, 8H); 7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): 31.60 (t), 43.83 (t), 64.37 (d), 66.03 (d), 77.74 (d), 126.08 (d), 127.93 (d), 128.03 (2C, d), 128.34 (2C, d), 128.41 (2C, d), 128.55 (2C, d), 136.40 (s), 140.98 (s), 159.55 (s, C=O). Mass (*m*/*z*): 326 (M^+, 25), 308 (19), 280 (13), 192 (9), 187 (19), 160 (6), 147 (5), 132 (27), 121 (36), 104 (23), 91 (100), 77 (14), 65 (6).

4.1.4. (3*S*,7a*R*)-6-Benzyl-7-methoxy-3-phenyltetrahydro-5*H*-imidazo[1,5-*c*][1,3]thiazol-5-one (6). To hydroxy imidazothiazolone **5** (32.6 g, 0.1 mol) dissolved in anhydrous methanol (300 mL) was added cat. amount of *p*-TSA and the reaction mixture was stirred at room temperature for 10 min. After completion of the reaction (by TLC) the reaction mixture was quenched with solid sodium carbonate and filtered. Removal of solvent and extraction with EtOAc furnished the methoxy imidazothiazolone **6**. Yield: 33.8 g (99%). Mp 83 °C, $[\alpha]_D$ −210 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 2930, 1705, 1510, 1420, 1360, 1236, 1160, 1005. ^1H NMR ($CDCl_3$, 200 MHz): 2.55 (t, 1H, *J*=9.75 Hz); 3.13 (dd, 1H, *J*=4.87, 12.19 Hz); 4.0 (dd, 1H, *J*=4.87, 9.75 Hz); 3.30 (s, 3H); 4.21 (d, 1H, *J*=15.14 Hz); 4.65 (s, 1H); 4.90 (d, 1H, *J*=15.14 Hz); 6.45 (s, 1H); 7.38 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 36.39 (t), 44.60 (t), 52.96 (q), 64.79 (d), 65.37 (d), 86.87 (d), 126.0 (d), 127.65 (d), 127.73 (d), 127.82 (d), 128.13 (d), 128.29 (2C, d), 128.42 (d), 128.55 (d), 128.70 (d), 136.12 (s), 141.36 (s), 160.01 (s, C=O). Mass (*m*/*z*): 340 (M^+, 24), 309 (6), 294 (54), 240 (6), 203 (19), 187 (5), 174 (13), 144 (6), 132 (42), 121 (8), 106 (33), 91 (100), 77 (13), 65 (6). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Found: C, 67.10; H, 5.87; N, 8.56; S, 8.90.

4.2. General procedure for the reductive cleavage of C–S bond of methoxy imidazothiazolone 6

(*A*) *By using tri-n-butyltin hydride*. A solution of methoxy imidazothiazolone **6** (0.34 g, 1.0 mmol), tributyltin hydride (0.349 g, 1.2 mmol) and AIBN (50 mg) in dry benzene (4 mL) was refluxed for 30 min with addition of few crystals (10 mg) of AIBN at the end of every 10 min. The progress of the reaction was monitored by TLC. After completion of reaction, the organic solvent was evaporated and the crude reaction mixture was stirred with chloro compound (1.0 mmol) and anhydrous potassium carbonate (0.414 g, 0.3 mmol) in anhydrous acetone (10 mL) for 10–12 h at room temperature. Filtration and evaporation of organic solvent furnished a residue, which was column chromatographed on silica gel using 35% ethyl acetate:pet. ether as eluent to furnish *S*-alkylated compounds.

(*B*) *By using Li/Arene*. To a cooled (−78 °C) suspension of lithium (0.0347 g, 0.011 mmol) and naphthalene (0.0034 g; 0.026 mmol) in tetrahydrofuran (20 mL) was added methoxy imidazothiazolone **6** (0.340 g, 1.0 mmol) in tetrahydrofuran (10 mL) and stirred for 3 h. The reaction mixture was quenched with water as an electrophile and allowed to warm to room temperature over a period of 1 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate. The organic layer was separated from filtrate and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure to furnish the crude residue, which was subjected to alkylation with halo compounds as mentioned in method A.

(*C*) *By using Zn/saturated NH_4Cl*. To a solution of methoxy imidazothiazolinone **6** (0.34 g, 1.0 mmol) in THF (7 mL) was added activated zinc (2 g, 30.5 mmol) and saturated aqueous ammonium chloride solution (7 mL). The mixture was stirred vigorously at 25 °C under nitrogen atmosphere. Progress of the reaction was monitored by TLC. After 12 h the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2×30 mL). The organic layer was washed with two 20 mL portions of saturated aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude mass was subjected to S-alkylation with alkyl halides as mentioned in method A.

4.2.1. Methyl ({[(4*R*)-1,3-dibenzyl-5-methoxy-2-oxoimidazolidin-4-yl]methyl}thio)acetate (7a). Yield: 0.386 g (80%). $[\alpha]_D$ −18.4 (*c* 1.04, $CHCl_3$) IR (neat, cm^{-1}): 3006, 2930, 1725, 1701, 1450, 1358, 1234, 1077. ^1H NMR ($CDCl_3$, 200 MHz): 2.50 (dd, 1H, *J*=8.3, 12.50 Hz); 2.71 (dd, 1H, *J*=4.16, 12.50 Hz); 2.87 (s, 2H); 3.01 (s, 3H); 3.58 (dd, 1H, *J*=4.16, 8.3 Hz); 3.64 (s, 3H); 4.0 (d, 1H, *J*=15.46 Hz); 4.31 (d, 1H, *J*=15.46 Hz); 4.52 (d, 1H, *J*=15.34 Hz); 4.57 (s, 1H); 5.11 (d, 1H, *J*=15.46 Hz); 7.36 (m, 10H). Mass (*m*/*z*): 414 (M^+, 1), 399 (1), 382 (3), 309 (5), 295 (15), 277 (10), 203 (2), 181 (5), 161 (4), 132 (5), 117 (2), 105 (6), 91 (100), 77 (4), 65 (14).

4.2.2. ({[(4*R*)-1,3-Dibenzyl-5-methoxy-2-oxoimidazolidin-4-yl]-methyl}thio)acetonitrile (7c). Yield: 0.297 g (78%). $[\alpha]_D$ +49.73 (*c* 1.0, $CHCl_3$) IR (neat, cm^{-1}): 2925, 2230, 1703, 1463, 1359, 1237, 1077. ^1H NMR ($CDCl_3$, 200 MHz): 2.62 (dd, 1H, *J*=7.54, 11.32 Hz); 2.80 (dd, 1H, *J*=3.89, 11.32 Hz); 3.03 (s, 3H); 3.05 (s, 2H); 3.45 (m, 1H); 4.15 (dd, 2H, *J*=15.10 Hz); 4.50 (d, 1H, *J*=1.3 Hz); 4.90 (dd, 2H, *J*=15.10 Hz); 7.35 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz): 17.12 (t), 33.3 (t), 44.6 (t), 45.5 (t), 52.3 (q), 56.3 (d), 88.1 (d), 116.0 (s), 127.5 (d), 127.8 (2C, d), 128.2 (3C, d), 128.5 (2C, d), 128.8 (2C, d), 136.4 (s), 136.8 (s), 158.2 (s, C=O). Mass (*m*/*z*): 381 (M^{+1}, 1), 361 (1), 349 (1), 295 (18), 277 (4), 269 (4), 257 (1), 233 (4), 204 (3), 187 (3), 177 (15), 162 (3), 149 (4), 134 (6), 121 (9), 106 (10), 91 (100), 77 (4), 65 (13). Anal. Calcd for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01; S, 8.41. Found: C, 66.30; H, 5.85; N, 10.82; S, 8.65.

4.2.3. (4*R*)-4-[(Allylthio)methyl]-1,3-dibenzyl-5-methoxyimidazolidin-2-one (7d). Yield: 0.325 g (85%). $[\alpha]_D$ +41.3 (*c* 1, $CHCl_3$) IR (neat, cm^{-1}): 3062, 3026, 2922, 1709, 1620, 1494, 1424, 1356, 1224, 1094, 1029. ^1H NMR ($CDCl_3$, 200 MHz): 2.21 (dd, 1H, *J*=9.28, 13.68 Hz); 2.58 (dd, 1H, *J*=3.90, 13.68 Hz); 2.93 (d, 2H, *J*=7.33 Hz); 3.07 (s, 3H); 3.33 (m, 1H, *J*=3.90, 9.28 Hz); 4.08 (d, 1H, *J*=15.62 Hz); 4.10 (d, 1H, *J*=15.62 Hz); 4.47 (d, 1H, *J*=0.97 Hz); 4.91 (m, 4H); 5.58 (m, 1H); 7.29 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz): 30.92 (d), 35.01 (d), 44.53 (q), 52.34 (2C, t), 56.77 (t), 88.24 (t), 117.53 (t), 127.36 (d), 127.48 (d), 127.61 (d), 127.94 (d), 128.21 (2C, d), 128.46 (2C, d), 128.67 (d), 133.78 (d), 137.02 (s), 137.16 (s), 159.73 (s, C=O). Mass (*m*/*z*): 382 (M^{+1}, 1), 362 (1), 351 (1), 295 (18), 277 (4), 269 (4), 257 (1), 233 (4), 162 (3), 149 (4), 134 (6), 121 (9), 106 (10), 91 (100), 77 (4), 65 (13). Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32; S, 8.38. Found: C, 69.30; H, 6.55; N, 7.65; S, 8.59.

4.2.4. Methyl ({[(4*S*)-1,3-dibenzyl-2-oxo-5-(phenylthio)-imidazolidin-4-yl]methyl}thio)acetate (8). Methoxy imidazolidine **7** (4.14 g, 10 mmol) was dissolved in thiophenol (20 mL) and the solution was cooled to 0 °C.

To this was then added cat. amount of *p*-TSA (20 mg, 0.1 mmol) and the mixture was stirred at 0 °C for 5 min. Mixture of DCM (20 mL) and water (5 mL) was added to reaction mixture, organic layer was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. Rotary evaporation of solvent under reduced pressure and chromatographic purification (20% ethyl acetate:pet. ether) afforded 4-thiophenoxy-imidazolidine **8**. Yield: 4.70 g (93%). $[\alpha]_D$ −19.36 (*c* 0.98; $CHCl_3$) IR (neat, cm^{-1}): 3030, 2920, 2875, 1725, 1695, 1583, 1495, 1420, 1386, 1365, 1064. ^1H NMR ($CDCl_3$, 200 MHz): 2.53 (dd, 1H, *J*= 14.0, 7.5 Hz); 2.70 (dd, 1H, *J*=14.0, 3.7 Hz); 2.9 (s, 2H); 3.60 (ddd, 1H, *J*=3.7, 3.7, 7.5 Hz); 4.0 (d, 1H, *J*=15.5 Hz); 3.65 (s, 3H); 4.3 (d, 1H, *J*=15.5 Hz); 4.53 (d, 1H, *J*= 15.0 Hz); 4.57 (d, 1H, *J*=3.7 Hz); 5.1 (d, 1H, *J*=15.0 Hz); 7.09 (m, 3H); 7.28 (m, 12H). Mass (*m/z*): 383 (M^+ −109, 18), 277 (100), 264 (7), 187 (7), 110 (7), 91 (54). Anal. Calcd for $C_{27}H_{28}N_2O_3S_2$: C, 65.83; H, 5.73; N, 5.69; S, 13.02. Found: C, 65.63; H, 5.53; N, 5.39; S, 12.91.

4.2.5. ({[(4*S*)-1,3-Dibenzyl-2-oxo-5-(phenylthio)imidazolidin-4-yl]methyl}thio)acetaldehyde (9). Thiophenoxy methyl ester **8** (2.21 g, 4.37 mmol) was taken in a 100 mL two-necked round bottom flask along with 30 mL of anhydrous toluene under an atmosphere of argon. The flask was cooled to −78 °C and DIBAL-H (0.68 g, 4.8 mmol) was added slowly at −78 °C and was stirred for 2 h. After 2 h (TLC) it was quenched with 2.0 mL of MeOH and 2.0 mL of water. The solution was then stirred for half an hour and the white solid thus obtained was filtered. The filtrate was evaporated under reduced pressure and the residue taken in EtOAc and washed with water. The organic layer was then dried over anhydrous Na_2SO_4, filtered and the product obtained was chromatographed on silica gel with 25% ethyl acetate:pet. ether to yield the product aldehyde **9** (1.57 g) in 78% as a colorless viscous liquid. $[\alpha]_D$ −26.7 (*c* 0.9, $CHCl_3$) IR (neat, cm^{-1}): 3010, 2900, 1710, 1700, 1600, 1580, 1495, 1450, 1390, 1140, 1070. ^1H NMR ($CDCl_3$, 200 MHz): 2.32 (m, 2H); 2.80 (d, 2H, *J*=3.6 Hz); 3.45 (m, 1H); 3.94 (d, 1H, *J*=15.2 Hz); 4.27 (d, 1H, *J*=15.2 Hz); 4.40 (d, 1H, *J*=15.2 Hz); 4.48 (d, 1H, *J*=4 Hz); 5.10 (d, 1H, *J*=15.2 Hz); 7.13 (m, 15H); 9.14 (t, 1H). Mass (*m/z*): 353 (M^+ −109, 5), 294 (6), 149 (5), 141 (7), 132 (14), 91 (100), 84 (11), 77 (17), 69 (13), 65 (18).

4.2.6. (5*R*)-1,3-Dibenzyl-4-methoxy-5-[({(*E*/*Z*)-2-[(trimethyl-silyl)oxy]vinyl}thio)methyl]imidazolidin-2-one (10). A solution of *t*-butyldimethylsilyl chloride (0.255 g, 1.69 mmol) in anhydrous DCM (5 mL) was added via syringe to a solution of aldehyde **9** (0.650 g, 1.41 mmol) in DCM (20 mL). After 5 min, DBU (0.28 g, 1.3 mmol) was added dropwise and mixture was heated to reflux. After 30 min (TLC) the reaction mixture was concentrated and purified by column chromatography eluting with 10% ethyl acetate:pet. ether to furnish 0.65 g, (80%) of TBS enol ether as a semi solid. IR (neat, cm^{-1}): 2910, 2840, 1695, 1600, 1595, 1450, 1420, 1375, 1210, 1100, 940. ^1H NMR ($CDCl_3$, 200 MHz): 0.1 (s, 6H); 0.8 (s, 9H); 2.20 (dd, 1H, *J*=7.0, 13.0 Hz); 2.40 (dd, 1H, *J*=4.0, 13.0 Hz); 3.40 (m,1H); 3.90 (d, 1H, *J*=15.0 Hz); 4.20 (d, 1H, *J*=15.0 Hz); 4.30 (d, 1H, *J*=15.0 Hz); 4.55 (d, 1H, *J*=3.5 Hz); 5.0 (d, 1H, *J*= 15.0 Hz); 5.15 (d, 1H, *J*=11.6 Hz); 6.56 (d, 1H, *J*= 11.6 Hz); 7.0 (m, 3H); 7.35 (m, 12H). Mass (*m/z*): 467 (M^+ −109, 5), 277 (40), 203 (7), 110 (29), 91 (100), 73 (28), 65 (13). Anal. Calcd for $C_{32}H_{40}N_2O_2S_2Si$: C, 66.62; H, 6.99; N, 4.86; S, 11.12. Found: C, 66.40; H, 6.78; N, 4.70; S, 11.01.

4.2.7. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-4-({[*tert*-butyl(dimethyl)-silyl]oxy}methyl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (11). A solution of phenylthio enol ether **10** (0.30 g, 0.52 mmol), tributyltin hydride (0.18 g, 0.63 mmol) and AIBN (cat.) in dry benzene (20 mL) was refluxed for 4 h with addition of few crystals of AIBN at the end of 2 h. After removal of benzene under reduced pressure, crude product thus obtained was purified by column chromatography (SiO_2) (10% ethyl acetate:pet. ether) to furnish the bicyclic silyl ether **11** (0.13 g, 53%) as a viscous liquid. $[\alpha]_D$ +46.2 (*c* 1.09, $CHCl_3$) IR (neat, cm^{-1}): 2910, 2840, 1690, 1600, 1580, 1495, 1460, 1360, 1250, 1100. ^1H NMR ($CDCl_3$, 200 MHz): 0.01 (s, 6H); 0.78 (s, 9H); 2.90 (d, 2H, *J*=2.0 Hz); 3.28 (dd, 1H, *J*=4.8, 8.1 Hz); 3.40 (dd, 1H, *J*=8.1, 10.1 Hz, CH_2–OTBS); 3.50 (dd, 1H, *J*=4.8, 10.1 Hz, C*H*$_2$–OTBS); 4.09 (m, 2H); 4.17 (d, 1H, *J*=15.0 Hz); 4.24 (d, 1H, *J*=15.0 Hz); 4.75 (d, 1H, *J*= 15.4 Hz); 4.80 (d, 1H, *J*=15.4 Hz); 7.25 (m, 10H). Mass (*m/z*): 468 (M^+, 8), 453 (21), 435 (4), 411 (90), 91 (100). Anal. Calcd for $C_{26}H_{36}N_2O_2SSi$: C, 66.62; H, 7.74; N, 5.98; S, 6.87. Found: C, 66.40; H, 7.68; N, 5.68; S, 6.76.

4.2.8. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-4-(hydroxymethyl) tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (12). To TBDMS ether **11** (0.312 g, 0.66 mmol) dissolved in anhydrous dichloromethane (10 mL) under nitrogen atmosphere was added borontrifluoride etherate (0.473 g, 3.3 mmol). After stirring at room temperature (2 h), the reaction mixture was neutralized with 1 M $NaHCO_3$ solution and extracted with DCM (2×10 mL). Combined organic layers were washed with water (2×10 mL), brine, dried over anhydrous Na_2SO_4, filtered and chromatographed (SiO_2) to furnish the alcohol **12** (0.177 g, 75%) as a viscous liquid. $[\alpha]_D$ +60.38 (*c* 2, $CHCl_3$) IR (neat, cm^{-1}): 3400, 2910, 1690, 1600, 1505, 1480, 1380, 1260, 1100. ^1H NMR ($CDCl_3$, 200 MHz): 2.20 (br s, 1H, D_2O exchangeable); 2.69 (dd, 1H, *J*=4.6, 10.6 Hz); 2.71 (dd, 1H, *J*=5.1, 10.6 Hz); 3.30 (s, 2H); 3.83 (d, 1H, *J*=8.1 Hz); 4.01 (m, 2H); 4.07 (d, 1H, *J*=15.0 Hz); 4.08 (d, 1H, *J*=15.4 Hz); 4.71 (app. t, 2H, *J*=15.4 Hz); 7.30 (m, 10H). Mass (*m/z*): 354 (M^+, 22), 307 (7), 277 (23), 263 (20), 187 (9), 149 (7), 91 (100), 65 (13), 57 (10). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05. Found: C, 67.40; H, 6.28; N, 7.70; S, 8.95.

4.2.9. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-2-oxohexahydro-1*H*-thieno-[3,4-*d*]imidazole-4-carbaldehyde (13). To a flame dried 50 mL round bottom flask equipped with a magnetic stirrer under nitrogen atmosphere was added dichloromethane (5 mL, freshly distilled over P_2O_5). The flask was cooled to −78 °C and oxalyl chloride (0.050 g, 0.395 mmol) was added, followed by DMSO (0.061 g, 0.790 mmol). After the mixture was stirred at −78 °C, a solution of alcohol **12** (0.070 g, 0.197 mmol) in DCM (2 mL) was added by syringe. The resulting cloudy solution was stirred at −78 °C for 1 h. Et_3N (0.12 g, 1.185 mmol) was added and the milky white solution was stirred for

30 min at −78 °C. Reaction mixture was allowed to warm gradually to ambient temperature. After 2 h, water (10 mL) was added and the organic layer was separated, washed with saturated aqueous NH_4Cl (2 mL), aqueous $NaHCO_3$ (2 mL), and brine (5 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure and chromatographic purification (SiO_2) of the residue (25% ethyl acetate:pet. ether) furnished aldehyde **13** as a solid (0.043 g, 61%). Mp 140–141 °C, $[\alpha]_D$ −62.4 (*c* 0.75, $CHCl_3$) IR (neat): 3120, 2940, 1720, 1695, 1605, 1595, 1500, 1450, 1250. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.29 (dd, 1H, *J*=4.7, 13.2 Hz); 2.68 (dd, 1H, *J*=4.7, 13.2 Hz); 3.59 (s, 1H); 4.11 (dd, 1H, *J*=4.7, 7.8 Hz); 4.16 (d, 1H, *J*=15.4 Hz); 4.34 (d, 1H, *J*=7.9 Hz); 4.36 (d, 1H, *J*=15.4 Hz); 4.47 (d, 1H, *J*=15.4 Hz); 4.68 (d, 1H, *J*=15.4 Hz); 7.25 (m, 10H); 9.13 (s, 1H). Mass (*m*/*z*): 352 (M^+, 5), 323 (5), 277 (93), 264 (6), 91 (100), 65 (6). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.1. Found: C, 67.73; H, 6.06; N, 7.81; S, 9.35.

4.2.10. Methyl 5-[(3a*S*,4*S*,6a*R*)-1,3-dibenzyl-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]-5-hydroxypentanoate (14). Under nitrogen atmosphere, magnesium (0.061 g, 2.54 mmol) turnings were initially introduced into THF (10 mL) and the mixture was heated to boiling. A solution of dibromopropane (0.516 g, 2.54 mmol) in THF (10 mL) was added to this suspension during 30 min. The reaction mixture was heated to reflux for 45 min and subsequently stirred at room temperature for 12 h. It was then cooled to −15 °C and a solution of cyclic aldehyde **13** (0.18 g, 0.51 mmol) in THF (10 mL) was added dropwise in the course of 30 min at a temperature between −14 and −16 °C. After stirring for 10 min the reaction vessel was evacuated and charged with CO_2 atmosphere. To this reaction mixture solid carbon dioxide (~1 g) was added. After 1 h, dil HCl (1 N, 5 mL) was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water (20 mL), brine (20 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the crude product was subjected to esterification with diazomethane. Chromatographic purification of the residue (50% ethyl acetate:pet. ether) furnished hydroxy methyl ester **14** (0.176 g, 76%); as a viscous liquid. IR (neat, cm^{-1}): 3310, 3032, 2928, 1743, 1700, 1440, 1342, 1231, 1079, 789. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.25 (m, 2H); 1.59 (m, 2H); 2.22 (t, 2H, *J*=7.3 Hz); 2.70 (dd, 1H, *J*=2.4, 12.2 Hz); 2.91 (dd, 1H, *J*=1.5, 12.2 Hz); 3.20 (m, 1H, *J*=1.5 Hz); 3.28 (br s, 1H); 3.64 (s, 3H); 3.94 (dd, 1H, *J*=7.8, 8.3 Hz); 4.06 (m, 2H); 4.12 (d, 1H, *J*=15.6 Hz); 4.21 (d, 1H, *J*=15.6 Hz); 4.73 (d, 1H, *J*=15.1 Hz); 4.75 (d, 1H, *J*=15.1 Hz); 7.28 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 20.97 (t), 33.48 (t), 35.07 (t), 36.23 (t), 46.27 (t), 46.82 (t), 51.52 (q), 59.49 (d), 62.39 (d), 65.65 (d), 71.63 (d), 127.51 (d), 127.60 (d), 127.97 (2C, d), 128.03 (2C, d), 128.61 (2C, d), 128.67 (2C, d), 136.97 (2C, s), 159.31 (s, C=O), 173.66 (s, C=O). Mass (*m*/*z*): 454 (M^+, 5), 407 (4), 363 (11), 324 (33), 277 (55), 233 (11), 187 (21), 149 (14), 91 (100), 65 (11). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16; S, 7.05. Found: C, 66.12; H, 6.36; N, 5.98; S, 6.87.

4.2.11. Methyl (5*E*/*Z*)-5-[(3a*S*,6a*R*)-1,3-dibenzyl-2-oxohexahydro-4*H*-thieno[3,4-*d*]imidazol-4-ylidene] pentanoate (15). The hydroxy ester **14** (0.15 g, 0.330 mmol) was dissolved in anhydrous DCM (20 mL), cooled to 0 °C and triethyl amine (0.067 g, 0.33 mmol), added. To this reaction mixture MsCl (0.045 g, 0.393 mmol) was added and mixture was stirred at room temperature for 3 h, then diluted with water, and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with dil HCl, aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuum yielded 0.172 g (98%) of mesylate as a dark yellow viscous liquid.

The crude mesylate (0.170 g, 0.32 mmol) was dissolved in anhydrous DBU (0.486 g, 3.2 mmol) and heated to 60 °C for 12 h. After completion of reaction, the reaction mixture was acidified with dil HCl (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography of the residue over silica gel using ethyl acetate/pet. ether (35:65) mixture as eluent furnished the olefin **15** as pale yellow viscous liquid. Yield: (0.110 g, 80%); viscous liquid. $[\alpha]_D$ + 194 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3032, 2928, 1743, 1701, 1634, 1440, 1415, 1342, 1219, 1143, 1079, 789. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.72 (m, 2H); 2.12 (m, 2H); 2.31 (t, *J*=7.3 Hz, 2H); 3.05 (dd, *J*=9.2, 10.2 Hz, 1H); 3.12 (dd, *J*=4.4, 10.2 Hz, 1H); 3.70 (s, 3H); 4.05 (d, *J*=15.4 Hz, 1H); 4.10 (ddd, *J*=4.4, 7.3, 9.5 Hz, 1H); 4.25 (d, *J*=15.1 Hz, 1H); 4.30 (d, *J*=7.32 Hz, 1H); 4.85 (d, *J*=15.4 Hz, 1H); 5.01 (d, *J*=16.0 Hz, 1H); 5.54 (t, *J*=7.3 Hz, 1H); 7.35 (m, 10H). Mass (*m*/*z*): 436 (M^{+1}, 1), 422 (1), 405 (1), 345 (1), 309 (45), 263 (37), 187 (6), 173 (4), 158 (4), 143 (5), 132 (17), 117 (8), 105 (25), 91 (100), 77 (10), 65 (6).

4.2.12. Dibenzylbiotin methyl ester. A mixture of olefin **15** (0.100 g, 0.23 mmol) and 10% palladium on charcoal (10 mg) in methanol (20 mL) was hydrogenated (200 psi) at 65 °C for 8 h. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give the crude *N*,*N*′-dibenzyl biotin methyl ester, which was subjected to debenzylation without further purification. Mp 78–80 °C, $[\alpha]_D$ −42.13 (*c* 1.05, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3028, 2932, 2840, 1741, 1698, 1448, 1440, 1425, 1347, 1198, 1134, 1081, 792. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.67 (m, 6H); 2.33 (t, 2H); 3.10 (m, 1H); 3.69 (s, 3H); 3.90 (m, 3H); 4.15 (d, *J*=15.4 Hz, 1H); 4.75 (d, *J*=15.6 Hz, 1H); 5.10 (d, *J*=15.4 Hz, 1H); 7.32 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 24.42 (t), 28.14 (t), 28.29 (t), 33.65 (t), 34.53 (t), 46.40 (t), 47.76 (t), 51.25 (d), 54.05 (d), 60.99 (d), 62.46 (q), 127.42 (d, 2C), 128.04 (d, 4C), 128.45 (d, 4C), 136.79 (s, 2C); 160.83 (s, C=O), 173.66 (s, C=O). Mass (*m*/*z*): 438 (M^+, 8), 347 (13), 277 (31), 265 (13), 240 (9), 187 (18), 149 (4), 91 (100), 77 (3), 65 (9).

4.2.13. D-(+)-Biotin. *N*,*N*′-Dibenzyl biotin methyl ester (0.1 g, 0.23 mmol) was added to a solution of 47% hydrobromic acid (5 mL). The reaction mixture was stirred under reflux for 5 h. After cooling to room temperature, the reaction mixture was extracted with toluene (2×10 mL). The aqueous phase was concentrated under reduced pressure to dryness. The residue was dissolved in anhydrous methanol (5 mL) and refluxed for 2 h in the presence of concd H_2SO_4 (one drop). The reaction mixture was

neutralized with solid $NaHCO_3$, filtered and concentrated under reduced pressure. Crude solid thus obtained was dissolved in methanol (10 mL) and charcoal added, heated and filtered. The filtrate was concentrated under reduced pressure to furnish a residue, which was chromatographed to furnish a white solid. The solid was heated on a water bath with 1 N NaOH (10 mL) and the progress of the reaction monitored by TLC. The solvent was reduced to 5 mL and neutralized with concd HCl to pH 2. The white solid thus obtained was filtered and dried at 80 °C under vacuum to give pure **1** (0.041 g, 78%). Mp 230–231 °C (lit.[11] 229.5–230 °C), $[\alpha]_D+89.7$ (*c* 1.01, 0.1 N NaOH) lit.[11] $[\alpha]_D+91.3$ (*c*, 1.0, 0.1 N NaOH) IR (KBr, cm^{-1}): 3308, 2929, 1701, 1672. ^1H NMR ($CDCl_3$): δ 1.30–1.67 (m, 6H, 3×CH2); 2.14 (t, 2H, $J=7.3$ Hz); 2.62 (dd, 1H, $J=1.7$, 12.5 Hz); 2.78 (dd, 1H, $J=4.7$, 12.5 Hz); 3.16 (m, 1H); 4.19 (m, 1H); 4.28 (m, 1H); 6.41 (s, 1H, NH); 6.52 (s, 1H).

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References and notes

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