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A Rapid Synthesis of the Biotin Core through a Tandem Michael Reaction

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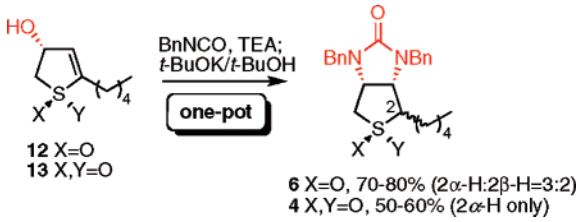
ABSTRACT



A biotin core has been assembled in a short and efficient sequence utilizing a tandem intramolecular Michael reaction/fragmentation/Michael reaction from vinyl sulfoxide and sulfone alcohols (12 and 13).

(+)-Biotin (**1**), known as vitamin H, is an essential ingredient in human metabolic cycles.[1] An early discovery of this water-soluble biocatalyst, participating in the reversible fixation of carbon dioxide in the biosynthesis of organic molecules, has attracted considerable interest in the synthetic community.[2] In addition to its important biological roles in human nutrition and animal health, biotinylation has allowed for identification and purification of the protein complement of cells in the genomic and postgenomic era.[3] One of the difficulties of using biotinylation in protein purification is due to the fact that biotin has the strongest noncovalent interaction known in nature with avidin ($K_d = 10^{-15}$ M).

Several approaches have been tested to facilitate the release of biotinylated targets from (strept)avidin complexes.[4] However, use of biotin derivatives that possess decreased affinity for (strept)avidin has not been extensively exploited due to the lack of a general synthetic approach to biotin analogues. To facilitate the recovery of the biotinylated target from (strept)avidin complexes, we have selected two variables in the biotin analogue structures: (1) the oxidation state of sulfur (**3**−**6**)[5] and (2) the stereochemistry of the valeryl chain (**2**, **4**−**6**).[6] Herein we report our preliminary results on a facile approach to the biotin core utilizing a one-pot tandem intramolecular Michael reaction from vinyl sulfoxide and sulfone alcohols.

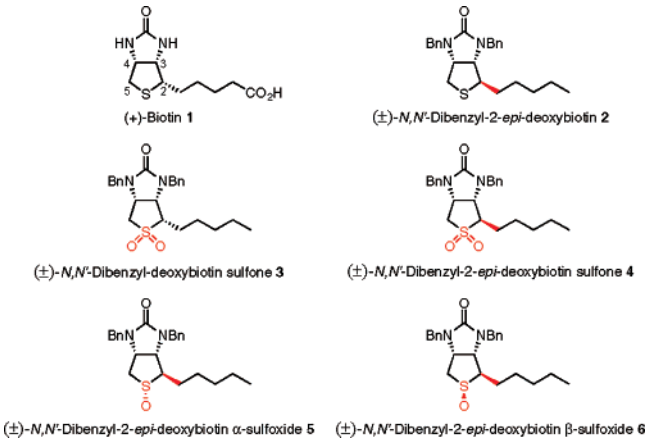


Figure 1. Structures of (+)-biotin and biotin analogues.

Our synthesis began with the Friedel−Crafts acylation of 1-heptyne **7** using α-chloroacetyl chloride in the presence of aluminum chloride to give 1,4-dichlorobut-3-en-2-one derivative **8**.[7] Simply mixing solid granules of sodium hydrosulfide hydrate in neat 1,4-dichlorobut-3-en-2-one derivatives **8** resulted in the *exclusive* formation of thiophen-

(1) Uskokovic, M. R. In *Encyclopedia of Chemical Technology*, 3rd ed.; Kirk, R. E., Othemr, D. E., Eds.; Wiley: New York, 1984; Vol. 24, p 41.

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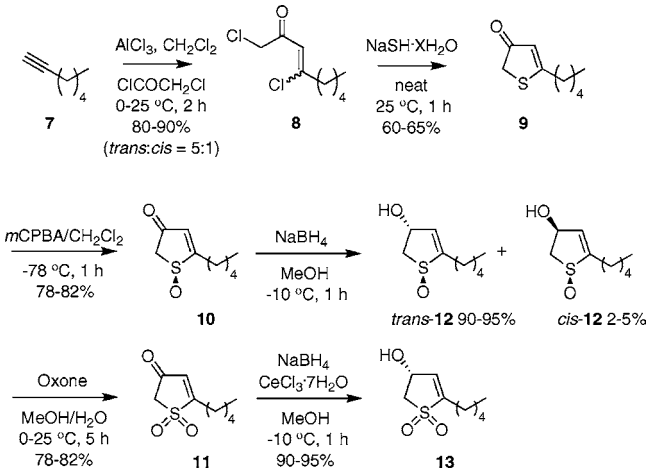
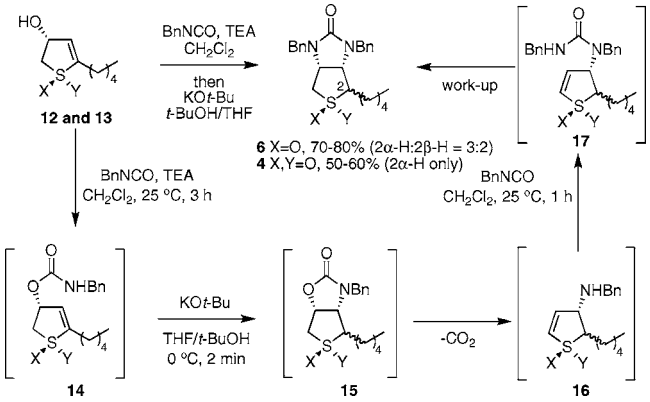
3-one **9**. The resulting product **9** was simply filtered through a plug of Celite to remove the excess solid reagent. It is worth noting that the preparation of the thiophen-3-one **9** is highly efficient and easily scalable without much complication.[8] The thiophen-3-one **9** is next converted to the corresponding sulfoxide **10** and sulfone derivative **11** by using *m*-chloroperbenzoic acid and Oxone, respectively. While attempted reduction of the thiophen-3-one **9** was unsuccessful under various conditions,[9] the reduction of thiophen-3-one oxide **10** and dioxide **11** with sodium borohydride gave clean reduction products (**12** and **13**) in excellent yield and selectivity.

Scheme 1. Synthesis of Thiophen-3-one Derivatives



The alcohols (**12** and **13**) were then converted to bicyclic urea (**4** and **6**) through a successive treatment of benzyl isocyanate and potassium *tert*-butoxide.[10] This tandem intramolecular Michael reaction/fragmentation/Michael reaction allows a facile entry to the requisite core of biotin.[11] Moreover, intermediates **14**, **16**, and **17** in Scheme 2 can be

Scheme 2. Synthesis of Biotin Skeleton



isolated and the stepwise reactions proceed in excellent yields (see the Supporting Information). Although the reaction gave low diastereoselectivity at the C_2 for sulfoxide **6** (sulfone **13** gave a 2α-H epimer **4** as the sole product),[12] the high chemical yield and the efficient chemical transformation are noteworthy.

To access *N*,*N*′-dibenzyl-2-*epi*-biotin **2**,[13] the deoxygenation of the 2,3-*trans*-sulfoxide **6** was performed with use of phosphorus trichloride in dichloromethane at low temperature.[14] Likewise, the 2,3-*cis*-sulfoxide **6a** yielded *N*,*N*′-dibenzyldeoxybiotin **18**[11] after reduction of a mixture of sulfide **18** and alkene **19**. A similar strategy has been applied to *cis*-sulfoxide **12** to give *N*,*N*′-dibenzyldeoxybiotin sulfoxides (**5** and **5a)** (see the Supporting Information). The debenzylation of the ureas (**2** and **18**) can be effected by the Hoffmann-La Roche protocol.[15]

(2) For the synthesis of biotin, see: (a) Chavan, S. P.; Chittiboyina, A. G.; Ramakrishna, G.; Tejwani, R. B.; Ravindranathan, T.; Kamat, S. K.; Rai, B.; Sivadasan, L.; Balkrishnan, K.; Ramalingam, S.; Deshpande, V. H. *Tetrahedron* **2005**, *61*, 9273. (b) Chen, F.-E.; Chen, X.-X.; Dai, H.-F.; Kuang, Y.-Y.; Xie, B.; Zhao, J.-F. *Adv. Synth. Catal.* **2005**, *347*, 549. (c) Mori, Y.; Seki, M. *Synlett* **2005**, 2233. (d) Chavan, S. P.; Chittiboyina, A. G.; Ravindranathan, T.; Kamat, S. K.; Kalkota, U. R. *J. Org. Chem.* **2005**, *70*, 1901. (e) Chavan, S. P.; Ramakrishna, G.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron Lett.* **2004**, *45*, 7307. (f) Seki, M.; Hatsuda, M.; Mori, Y.; Yoshida, S.; Yamada, S.; Shimizu, T. *Chem. Eur. J.* **2004**, *10*, 6101. (g) Kimura, M.; Seki, M. *Tetrahedron Lett.* **2004**, *45*, 1635. (h) Seki, M.; Kimura, M. *Yuki Gosei Kagaku Kyokaishi* **2004**, *62*, 882. (i) Chen, F.-E.; Dai, H.-F.; Kuang, Y.-Y.; Jia, H.-Q. *Tetrahedron*: *Asymmetry*, **2003**, *14*, 3667. (j) Seki, M.; Kimura, M.; Hatsuda, M.; Yoshida, S.; Shimizu. *Tetrahedron Lett.* **2003**, *44*, 8905. (k) Chen, F.-E.; Yuan, J.-L.; Dai, H.-F.; Kuang, Y.-Y.; Chu, Y. *Synthesis* **2003**, 2155. (l) Shimizu, T.; *Yakugaku Zasshi* **2003**, *123*, 43. (m) Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S. *J. Org. Chem.* **2002**, *67*, 5527. (n) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2002**, *43*, 1039. (o) Mori, Y.; Seki, M. *Heterocycles* **2002**, *58*, 125. (p) Seki, M.; Hatsuda, M.; Mori, Y.; Yamada, S. *Tetrahedron Lett.* **2002**, *43*, 3269. (q) Seki, M.; Shimizu, T.; Inubushi, K. *Synthesis* **2002**, 361. (r) Chavan, S. P.; Tejwani, R. B.; Ravindranathan, T. *J. Org. Chem.* **2001**, *66*, 6197. (s) Choi, C.; Tian, S.-K.; Deng, L. *Synthesis* **2001**, 1737. (t) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2000**, *41*, 5099. (u) Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Lett.* **1999**, *40*, 8873. (v) Zhou, Z.; Yang, H. *Huaxue Jinzhan* **1998**, *10*, 319. For a review on the synthesis of biotin, see: (w) DeClercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.

(3) (a) van Werven, F. J.; Timmers, H. T. *Nucleic Acids Res.* **2006**, *34*, e33. (b) Nguyen, G. H.; Milea, J. S.; Rai, A.; Smith, C. L. *Biomol. Eng.* **2005**, *22*, 147. (c) Chen, I.; Ting, A. Y. *Curr. Opin. Biotechnol.* **2005**, *16*, 35. (d) de Boer, E.; Rodriguez, P.; Bonte, E.; Krijgsveld, J.; Katsantoni, E.; Heck, A.; Grosveld, F.; Strouboulis, J. *Proc. Natl Acad. Sci. U.S.A.* **2003**, *100*, 7480 and references cited therein.

(4) Desarnaud, F.; Marie, J.; Larguier, R.; Lombard, C.; Jard, S.; Bonnafous, J.-C. *J. Chromatogr.* **1992**, *603*, 95 and reference cited therein.

(5) For the relative avidin binding affinity of biotin and its metabolites, see: (a) Sachon, E.; Tasseau, O.; Lavielle, S.; Sagan, S.; Bolbach, G. *Anal. Chem.* **2003**, *75*, 6536. (b) Zempleni, J.; Mock, D. M. *J. Nutr.* **1999**, *129*, 494S. (c) Finn, F. M.; Yamanouchi, K.; Titus, G.; Hofmann, K. *Bioorg. Chem.* **1995**, *23*, 152.

(6) Oh, K. *Tetrahedron Lett.* **2007**, *48*, 3685.

(7) Benson, W. R.; Pohland, A. E. *J. Org. Chem.* **1964**, *29*, 385.

(8) More detailed results will be published elsewhere.

(9) Low yield of the thiophene, presumably after dehydration, was obtained.

(10) For intramolecular conjugate addition of carbamates, see: (a) Wee, A. G. H.; McLeod, D. D.; Rankin, T. J. *Heterocycles* **1998**, *48*, 2263. (b) Clayden, J.; Nelson, A.; Warren, S. *Tetrahedron Lett.* **1997**, *38*, 3471. (c) Hirama, M.; Hioki, H.; Ito, S.; Kabuto, C. *Tetrahedron Lett.* **1988**, *29*, 3121. (d) Hirama, M.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125.

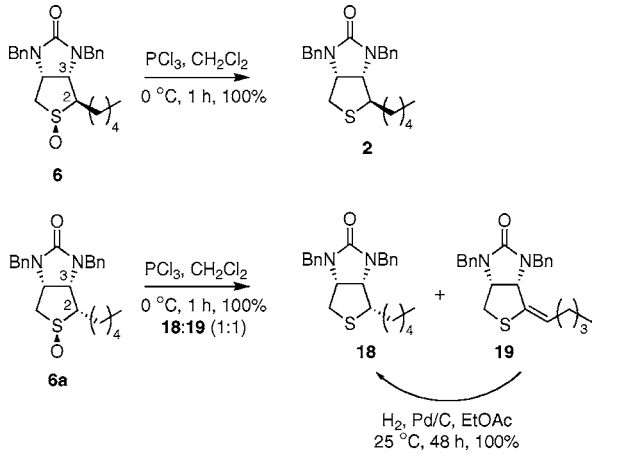
(11) For the synthesis of *N*,*N*′-dibenzyl-*cis*-ureylenesulfone from 2,5-dihydrothiophene *S*,*S*-dioxide, see: (a) Kotake, H.; Inomata, K.; Murata, Y.; Kinoshita, H.; Katsuragana, M. *Chem. Lett.* **1976**, 1073 (the reaction of 3,4-dibromosulfolane with benzylamine). (b) Ellis, F.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2866 (the intramolecular conjugate addition of the carbamate from 3,4-bromohydrinsulfolane).

(12) For the stereochemical assignment of hexahydrothienoimidazolone derivatives, see the Supporting Information.

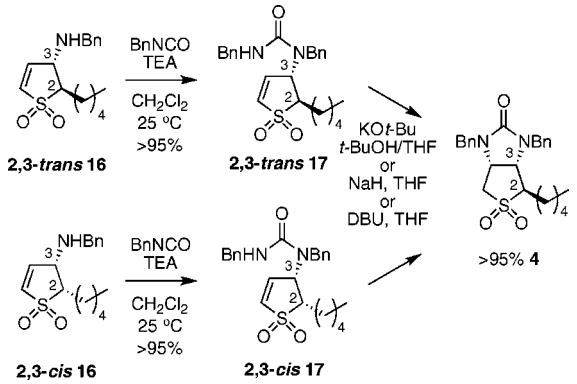
(13) Bates, H.; Rosenblum, S. *J. Org. Chem.* **1986**, *51*, 3447.

(14) Cere, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1986**, *51*, 4880.

Scheme 3. Synthesis of Deoxybiotin Derivatives



Scheme 4. Epimerization of *N*,*N*′-Dibenzyldeoxybiotin Sulfone



While the *trans*-sulfoxide alcohol **12** produced a mixture of diastereomers **6** and **6a**, a single diastereomer **4** was obtained from the sulfone alcohol **13**.[16] This serendipitous selectivity allows facile access to *N*,*N*′-dibenzyl-2-*epi*-biotin sulfone derivative **4**. To seek out the origin of this selectivity we isolated two allyl amine diastereomers **16** (2,3-*cis*/2,3-*trans*). As expected, a rapid epimerization was observed during the final Michael addition reaction to bicyclic biotin sulfone **4**.[17] Subjection of the 2,3-*cis*-sulfone **17** to other mild conditions such as sodium bicarbonate, sodium hydride in THF, or a catalytic amount of DBU in THF, while following reactions at regular intervals, failed to give the other isomeric species. Attemped epimerization of *N*,*N*′-dibenzyl-2-*epi*-deoxybiotin sulfone **4** under kinetic protonation also failed to give the biotin sulfone **3**.[18]

In conclusion, we have developed a rapid synthetic sequence to a biotin skeleton in six steps allowing a facile approach to biotin derivatives with varied oxidation states of the sulfur atom. The investigation into the asymmetric synthesis as well as the binding affinity assay of the prepared biotin derivatives to strept(avidin) is currently underway in our laboratory, and our results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710663

(15) Lee, H. L.; Baggiolini, E. G.; Uskokovic, M. R. *Tetrahedron* **1987**, *43*, 4887.

(16) Sulfone **3** can be obtained through oxidation of biotin derivative **18**, see ref 5.

(17) The sulfoxide **17** does not epimerize under identical conditions, the stereoselectivity of **6** was derived from the sulfoxide **16** (2,3-*trans*:2,3-*cis* = 3:2), see the Supporting Information.

(18) Treatment with LDA at −78 °C then *tert*-butanol quenching led to decomposion as well as the recovery of the starting material.