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Asymmetric synthesis of cytotoxic sponge metabolites *R*-strongylodiols A and B

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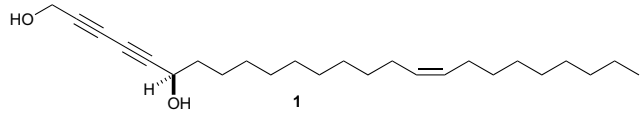
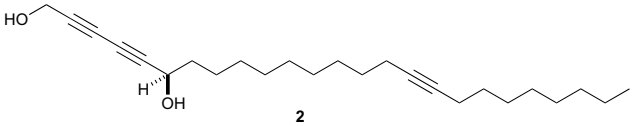
Abstract—The asymmetric synthesis of the marine sponge natural products, *R*-strongylodiols A **1** and B **2** using a minimum protection strategy is described. The chirality of the natural products was introduced via the Noyori asymmetric reduction of ynones.

Strongylodiols A **1**, B **2** and C **3** are three natural products isolated from the Okinawan marine sponge of the genus *Strongylophora* by Iguchi and co-workers.[1] The gross structures of **1**–**3** were determined by a combination of NMR and mass spectrometry analysis and through the application of the modified Mosher's method; compounds **1**–**3** were found to exist as enantiomeric mixtures (*R*/*S* ratio 91:9 for **1**, 97:3 for **2** and 84:16 for **3**) with the *R*-enantiomer as the major component in each compound. The enantiomeric mixtures of **1**–**3** were found to be cytotoxic towards MOTL-4, IMR-90 and DLD-1 cells. Previously Yadav and Mishra reported the synthesis of *R*-**2** via the β-elimination of a chiral epoxychloride[2] and recently Carreira and co-workers completed the syntheses of *R*-**1** and *R*-**2** through the addition of a chiral zinc acetylide to aldehydes.[3] We report here our effort in the asymmetric synthesis of *R*-**1** and **2** based on a minimum protection strategy. Retrosynthetically we envisaged that both *R*-**1** and **2** could be derived from the common intermediate **5**. We first investigated the synthesis of *R*-**2** due to its simpler structure.



1



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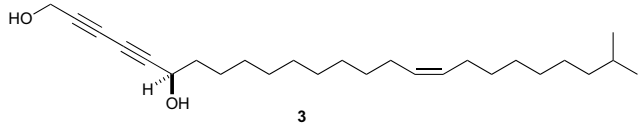

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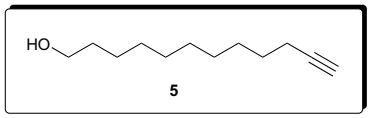

5

Commercially available 9-dodecyn-1-ol **4** was subject to a zipper reaction[4] using lithium 3-aminopropanamide in the presence of potassium *tert*-butoxide[5] to give 11-dodecyn-1-ol **5** in 92% yield. Alcohol **5** was treated with 2 equiv of *n*-BuLi in DMPU[6]/THF to generate the corresponding dianion, which was subsequently quenched with 1-iodooctane to afford alcohol **6** in 54% yield. Oxidation of alcohol **6** to aldehyde **7** was achieved in 86% yield with *o*-iodoxybenzoic acid (IBX) in THF/DMSO.[7] Addition of lithium trimethylsilylacetylide to aldehyde **7** gave *rac*-**8** in 86% yield, which was subjected to IBX oxidation to give ynone **9** in 87% yield. Asymmetric reduction of **9** with catalyst **10** in propan-2-ol delivered *R*-**8** in 90% yield.[8] The enantiomeric excess of *R*-**8** was 95% as determined by ^{19}F NMR analysis of its Mosher's ester.[9] The terminal trimethylsilyl group in

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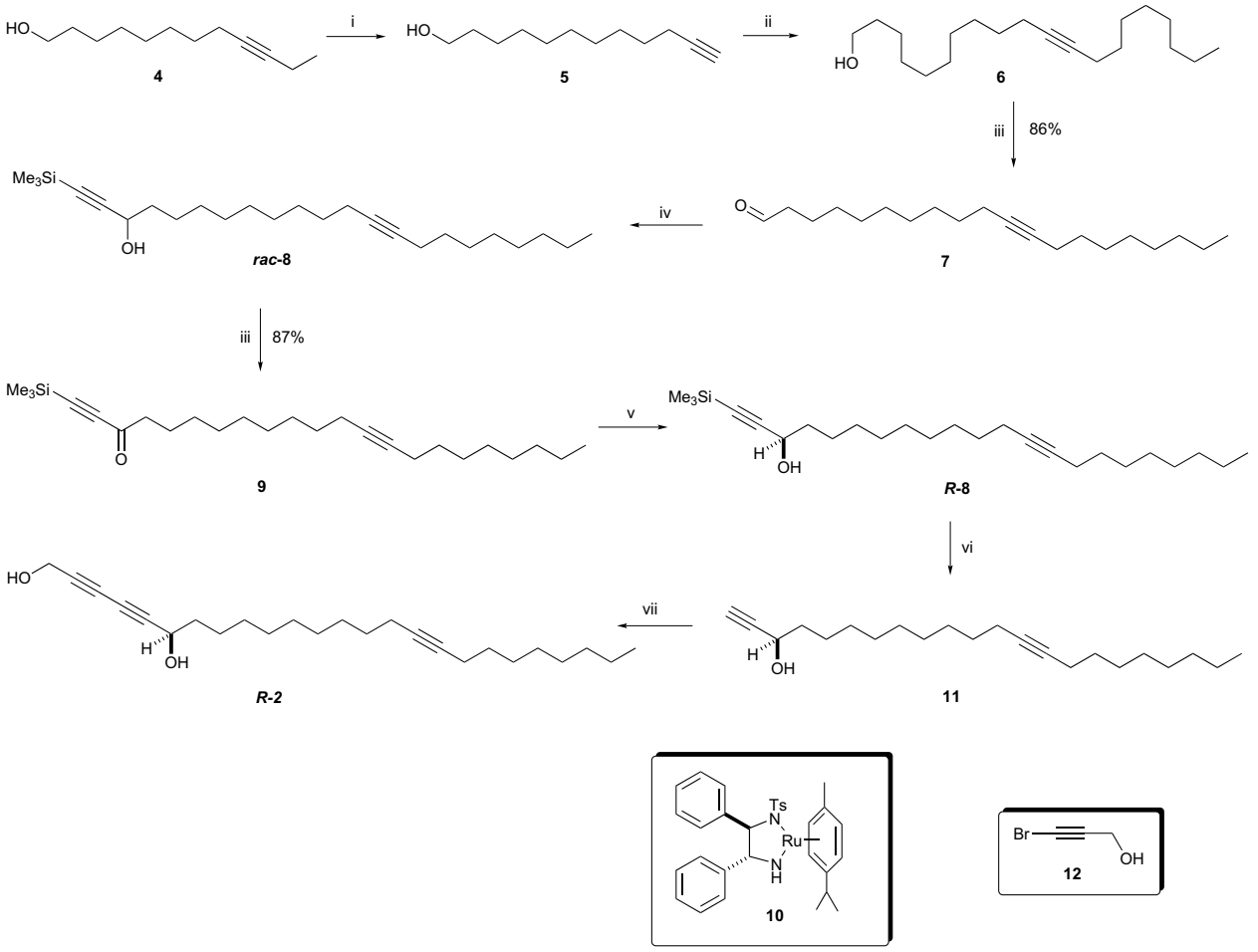
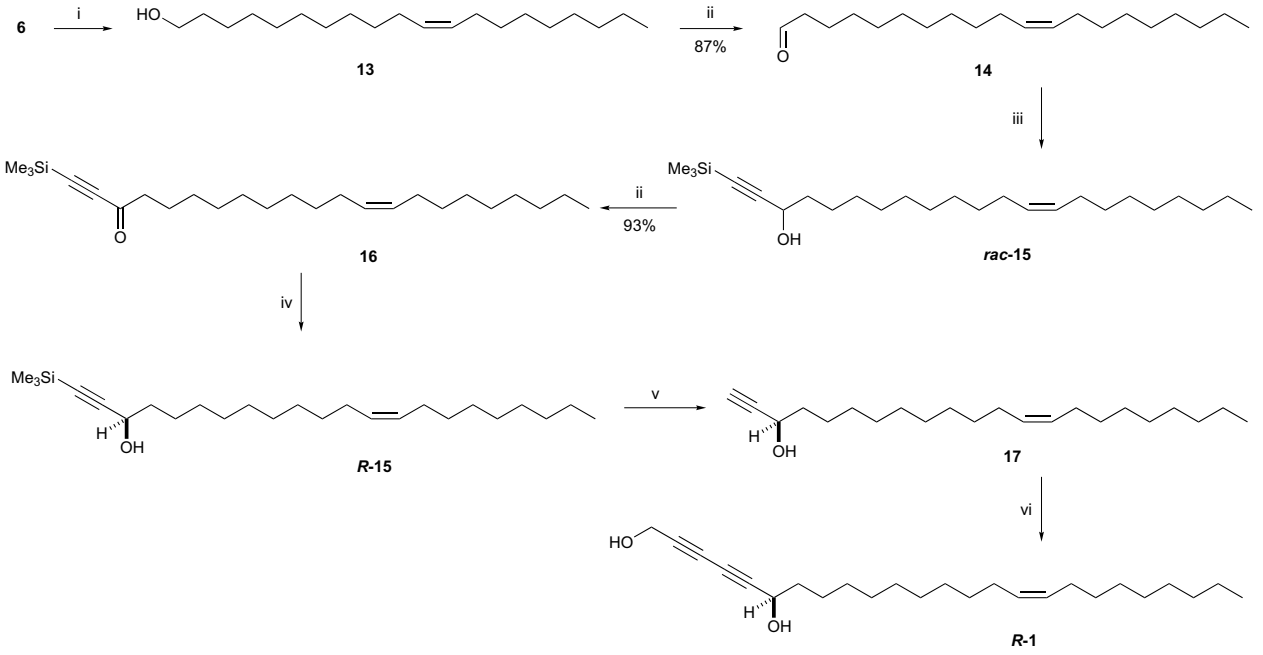


Scheme 1. Reagents and conditions: (i) $LiHN(CH_2)_3NH_2$, KO^tBu, $H_2N(CH_2)_3NH_2$, rt, 92%; (ii) *n*-BuLi (2 equiv), THF, DMPU, then $CH_3(CH_2)_7I$, 54%; (iii) IBX, DMSO, THF, rt; (iv) trimethylsilylacetylene, *n*-BuLi, THF, 86%; (v) **10**, *i*-PrOH, 30 °C, 90%; (vi) NH_4F, MeOH, 91%; (vii) **12**, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 82%.



Scheme 2. Reagents and conditions: (i) Lindlar catalyst, quinoline, H_2, benzene, 86%; (ii) IBX, DMSO, THF, rt; (iii) trimethylsilylacetylene, *n*-BuLi, THF, 76%; (iv) **10**, *i*-PrOH, 30 °C, 97%; (v) NH_4F, MeOH, 100%; (vi) **12**, CuCl, $NH_2OH{\cdot}HCl$, $EtNH_2$, MeOH, 80%.

R-**8** was removed by ammonium fluoride in methanol to afford **11** in 91% yield.[10] To the best of our knowledge there is currently no example of deprotection of a trimethylsilyl group from a terminal trimethylsilylacetylenic group using ammonium fluoride. Cadiot–Chodkiewicz coupling[11] of **11** and 2-bromopropyn-1-ol **12**[12] delivered *R*-**2** in 82% yield (Scheme 1).

The synthesis of **1** commenced with the Lindlar hydrogenation[13] of **6** to **13** in 86% yield, which was oxidised to aldehyde **14** in 87% yield by IBX in THF/DMSO.[7] Reaction of aldehyde **14** with lithium trimethylacetylide delivered *rac*-**15** in 76% yield. Oxidation of *rac*-**15** with IBX afforded a 93% yield of ynone **16** and subsequent chiral reduction of **16** with catalyst **10** in propan-2-ol gave *R*-**15** in 97% yield[8] with 95% ee.[9] Removal of the trimethylsilyl group from *R*-**15** was effected with ammonium fluoride[10] in methanol to deliver terminal acetylenic alcohol **17** in quantitative yield, which was coupled with **12** to afford *R*-**2** in 80% yield (Scheme 2).[11]

The spectral data and specific rotation values of both *R*-**1** and *R*-**2** are in excellent agreement with their corresponding literature values. In summary, we have developed an efficient synthesis of *R*-**1** and *R*-**2** without the deliberate use of protecting groups. We have also demonstrated that the Noyori reduction of ynones **9** and **16** were achieved with high yields and high enantiomeric excess. In addition, compound **5** could also be a useful intermediate for the synthesis of other members of the strongylodiols.[14]

Acknowledgements

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References and notes

1. Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T.; Van Soest, R. W. M. *Tetrahedron Lett.* **2000**, *41*, 9271–9276.
2. Yadav, J. S.; Mishra, R. K. *Tetrahedron Lett.* **2002**, *43*, 1739–1741.
3. Reber, S.; Knöpfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813–6817.
4. Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891–892.
5. Abrams, S. R.; Shaw, A. G. *Org. Synth. Coll. 8* **1993**, 146–148.
6. (a) Bengstoon, M.; Liljefors, T. *Synthesis* **1988**, *51*, 250–252; (b) Kaiser, A.; Marazano, C.; Mater, M. *J. Org. Chem.* **1999**, *64*, 3778–3782.
7. (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022; (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272–7276; (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
8. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
9. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
10. For the application of NH_4F in deprotection of silyl ethers, see: Zhang, W.; Robins, M. J. *Tetrahedron Lett.* **1992**, *33*, 1177–1180.
11. (a) Brandsma, L. *Preparative Acetylene Chemistry*. 2nd ed.; Elsevier: Oxford, 1988, Chapter 10, pp 212–230; (b) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
12. Polt, R.; Sames, D.; Chruma, J. *J. Org. Chem.* **1999**, *64*, 6147–6158.
13. Poulain, S.; Noiret, N.; Nugier-Chauvin, C.; Patin, H. *Liebigs Ann.* **1997**, 35–40.
14. Watanabe, K.; Tsuda, Y.; Yamane, Y.; Takahashi, H.; Iguchi, K.; Naoki, H.; Fujita, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*. 42nd ed.; Nippon Kagakka, 2000.