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Enantiospecific Total Synthesis of Macrolactone Sch 725674

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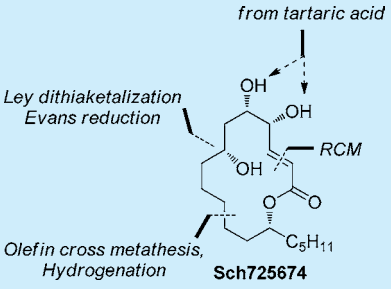
Supporting Information

ABSTRACT: The enantiospecific total synthesis of 14-membered macrolactone Sch 725674 was accomplished from tartaric acid. Key reactions in the synthesis include the Ley's dithiaketalization of an alkynone derived from the bis-Weinreb amide of tartaric acid, Boord olefination, and ring-closing metathesis of an acrylate ester.



Sch 725674 (**1**) is a 14-membered macrolactone isolated from the culture of *Aspergillus* by chemists at the Schering-Plough Co.[1] Structurally, the macrolactone possess three free hydroxy groups (two of them contiguous) and a (*E*)-α,β-unsaturated ester (Figure 1). A solitary total synthesis of Sch 725674 was reported by the Curran group using their trademark fluorous tagging technology, which also established the absolute stereochemistry of the chiral centers present in macrolactone.[2] Recently, we disclosed an approach to the macrolactone core of Sch 725674 from chiral furyl carbinol.[3] In continuation of our efforts, herein, we report the total synthesis of Sch 725674.

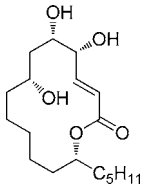
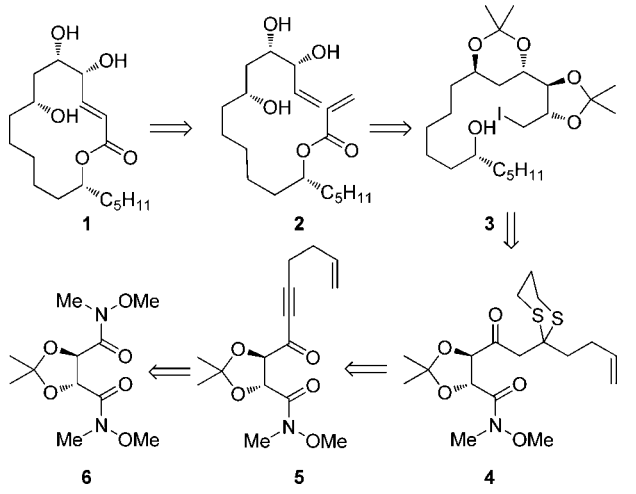


Figure 1. Macrolactone Sch 725674 (**1**).

We anticipated the formation of **1** by ring-closing metathesis of the acryloyl ester **2** possessing three free hydroxy groups. Although RCM is widely used for macrolactone formation, the use of acryloyl esters in the formation of macrolactones of a higher ring size is not so common.[4] Synthesis of the acryloyl ester **2** was envisaged from the iodide **3** via Boord olefination followed by subsequent deprotection of the 1,3-acetonide. The synthesis of **3** was planned by elaboration of the 1,3-dithianylketone **4**, the synthesis of which was envisioned by Ley dithiaketalization[5] of the alkynone in **5** with 1,3-propanedithiol. Desymmetrization of the bis-Weinreb amide **6** derived from tartaric acid by controlled addition of alkynyl Grignard reagent was envisaged for the synthesis of the alkynone **5** (Scheme 1).

Scheme 1. Retrosynthesis for Sch 725674 (1)



Accordingly, the synthetic sequence commenced with the addition of hex-5-en-1-ynylmagnesium chloride (prepared in situ from propargyl bromide and allylmagnesium chloride) to the bis-Weinreb amide **6**[6] to afford the alkynyl ketone **5** in 63% yield.[7] Ley's dithianylation[5] of the alkynyl ketone **5**, involving the addition of 1,3-propanedithiol, afforded the 1,3-dithianyl ketone in 97% yield. Olefin cross-metathesis of the alkene in **4** with the chiral homoallylic alcohol **7**[8] furnished the extended alkene **8** in 67% (87% brsm) yield.[9] Stereoselective reduction of the ketone in **8** with excess $NaBH_4$ not only afforded the secondary alcohol but also reduced the Weinreb amide to the corresponding primary alcohol to yield the triol **9** in 95% yield.[10] Deprotection of the dithiane in **9** using MeI/$CaCO_3$ produced the corresponding β-hydroxy ketone **10** which, on reduction with tetramethylammoniumtriacetoxy borohydride[11]

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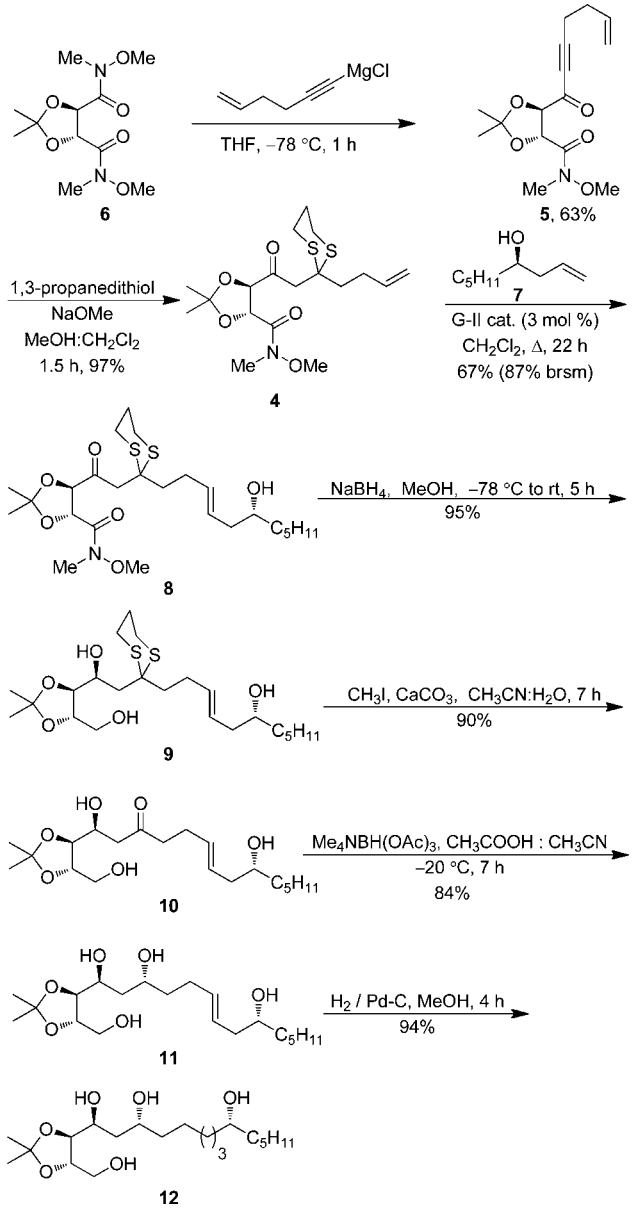
(Evans' reagent), furnished the 1,3-*anti*-diol **11** in 84% yield. Hydrogenation of the olefin in **11** produced the saturated tetrol **12** in 94% yield (Scheme 2).

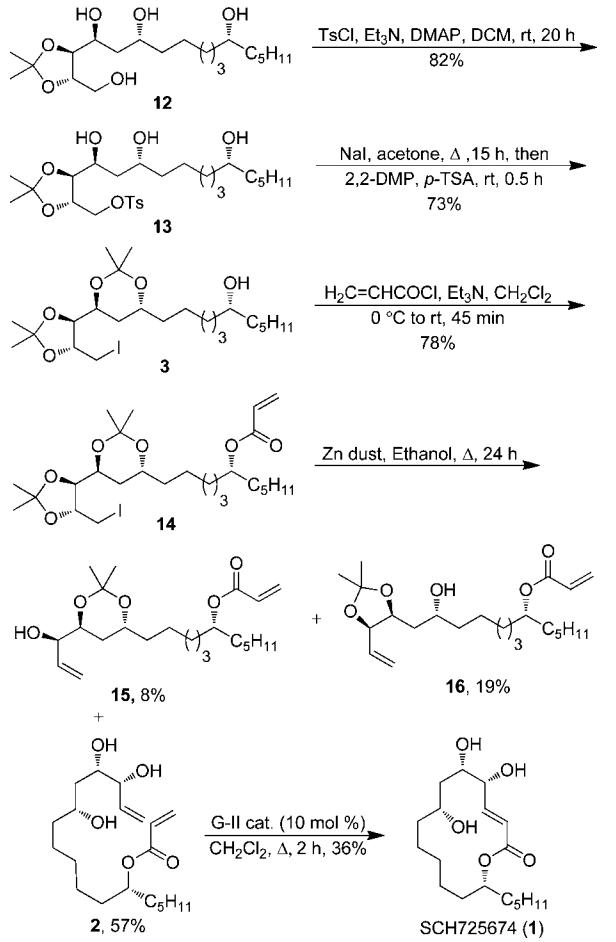
Scheme 2. Synthesis of the Tetrol 12



After successfully assembling the tetrol **12**, the primary alcohol in **12** was selectively transformed to the iodide **3**, via the formation of the tosylate **13**, iodination of the tosylate, and 1,3-diol protection as its corresponding acetonide in 73% yield. Acryloylation of the free alcohol in **3** furnished the acrylate **14** in 78% yield. The key Boord olefination reaction of **14** with zinc dust in ethanol at reflux produced the required acryloyl ester **2** in 57% yield along with the allyl alcohol **15** (8% yield) and the 1,2-acetonide **16** (19% yield). Ring-closing metathesis of the acryloyl ester **2** with Grubbs' second-generation catalyst furnished the macrolactone Sch 725674 (**1**) in 36% yield,[12] the spectral and physical data of which were in complete agreement with those reported by the Curran group[2] (Scheme 3).

In conclusion, the total synthesis of the macrolactone natural product Sch 725674 has been accomplished in 12 steps and

Scheme 3. Total Synthesis of Sch 725674 (1)



2.6% overall yield from the bis-Weinreb amide of tartaric acid. Key steps include the synthesis of a chiral alkynone from the desymmetrization of a tartaric acid amide with a functionalized alkynyl Grignard reagent and a Ley dithiaketalization of the alkynone. Ring-closing metathesis of the acryloyl ester was used to assemble the macrolactone.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of the NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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DEDICATION

This paper is dedicated with warmth and respect to Prof. Franklin A. Davis, Temple University, on the occasion of his 75th birthday.

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(4) For some examples of synthesis of macrolactones of ring size >10 by RCM of the acryloyl esters, see: (a) Lee, C. W.; Grubbs, R. H. *J. Org. Chem.* **2001**, *66*, 7155. (b) Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939. (c) Wang, B.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 5223. (d) Matsuya, Y.; Kobayashi, Y.; Kawaguchi, T.; Hori, A.; Watanabe, Y.; Ishihara, K.; Ahmed, K.; Wei, Z. L.; Yu, D. Y.; Zhao, Q. L.; Kondo, T.; Nemoto, H. *Chem.—Eur. J.* **2009**, *15*, 5799. (e) Jung, J. H.; Lee, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 5698. (f) Wang, B.; Hansen, T. M.; Weyer, L.; Wu, D.; Wang, T.; Christmann, M.; Lu, Y.; Ying, L.; Engler, M. M.; Cink, R. D.; Lee, C. S.; Ahmed, F.; Forsyth, C. J. *J. Am. Chem. Soc.* **2011**, *133*, 1506.

(5) (a) Snedden, H. F.; van den Heuvel, A.; Hirsch, A. K. H.; Booth, R. A.; Shaw, D. M.; Gaunt, M. G.; Ley, S. V. *J. Org. Chem.* **2006**, *71*, 2715. (b) Gaunt, M. J.; Sneddon, H. F.; Hewitt, P. R.; Orsini, P.; Hook, D. F.; Ley, S. V. *Org. Biomol. Chem.* **2003**, *1*, 15. (c) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003**, *5*, 1147. (d) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819.

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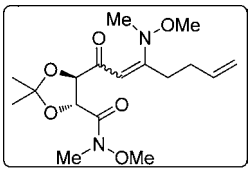
(7) Compound **5a** was also isolated in 23% yield in the reaction arising from the Michael addition of the released Weinreb amine to the ynone **5**.



5a

(8) Homoallylic alcohol **7** was prepared by Keck allylation of hexan-1-al with allyltributyltin according to the procedure described previously. (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (b) Also, see ref 3..

(9) The dimer resulting from the dimerization of the homoallylic alcohol **7** is also formed. See the Supporting Information for characterization of the dimer.

(10) Formation of the other diastereomer was not observed within detectable limits in ^{1}H NMR spectrum. Attempted selective reduction of the keto group in **8** was always accompanied by formation of the 1,4-diol **9**, and the purification was very cumbersome. Hence, both keto and the amide groups were reduced to the 1,4-diol **9** with excess $NaBH_4$.

(11) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

(12) Performing the reaction at higher dilution with the slow addition of either **2** to the catalyst or catalyst to the ester **2** (with the aid of syringe pump) did not improve the yield of the reaction. In addition, performing the reaction with Hoveyda–Grubbs' second-generation metathesis catalyst did not yield the desired product and resulted in a number of unidentifiable mixture of products.

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