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Ruthenium-SYNPHOS-Catalyzed Asymmetric Hydrogenations: an Entry to Highly Stereoselective Synthesis of the C15−C30 Subunit of Dolabelide A

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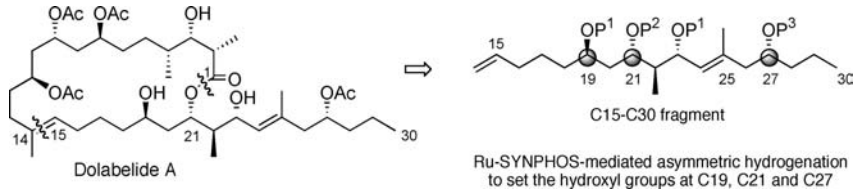
ABSTRACT



An efficient construction of the C15−C30 segment of the cytotoxic macrolide dolabelide A is described. The synthesis relies on ruthenium-SYNPHOS-mediated asymmetric hydrogenation reactions of β-keto esters to generate the C19, C21, and C27 hydroxyl-bearing stereocenters with very high levels of enantio- and diastereoselectivity.

The marine natural products dolabelides A and B have been isolated in 1995 from the Japanese sea hare *Dolabella auricularia* by Ojika and Yamada.[1] These 22-membered macrolides exhibit cytotoxic activity against HeLa-S_3 cells with IC_{50} values of 6.3 and 1.3 μg/mL, respectively. In 1997, the same group disclosed the closely related 24-membered congeners, dolabelides C and D,[2] from the same marine source. These compounds have also been shown to exhibit cytotoxicity against HeLa-S_3 cell lines with IC_{50} values of 1.9 and 1.5 μg/mL, respectively.

Common structural features of this class of macrolactones include two trisubstituted (*E*)-double bonds and eleven stereogenic centers, eight of which are hydroxyl or acetate functions. In view of their biological activity and structural complexity, as well as their limited availability from natural sources, several groups have been attracted by the synthetic challenge of the dolabelides,[3] including our group.[4] However, to date, only one total synthesis of dolabelide D has been accomplished by Leighton and co-workers.[5] As part of our ongoing projects involving the synthesis of biologically relevant natural products via ruthenium-promoted asymmetric hydrogenation,[6] we were particularly interested in the

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(2) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155–157.

(3) (a) Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419–421. (b) Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535–3537. (c) Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911–4914. (d) Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47*, 4075–4077. (e) Vincent, A.; Prunet, J. *Synlett* **2006**, 2269–2271. (f) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2007**, *9*, 4147–4150. (g) Waetzig, J. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 109–112. (h) Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 1421–1424.

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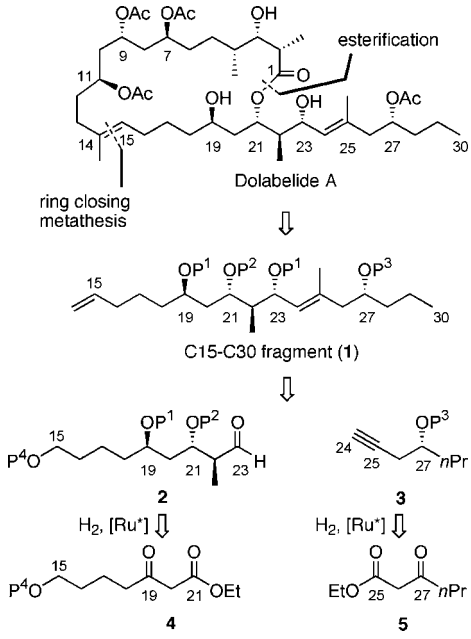
synthesis of dolabelide A because the C7−C11 and C19−C23 polypropionate/polyacetate motifs appeared ideally suited for construction through successive hydrogenation reactions. From a retrosynthetic point of view, dolabelide A can be disconnected into two fragments, C1−C14 and C15−C30, which would be assembled by esterification and ring-closing metathesis, a strategy successfully adopted by Leighton[5] (Scheme 1). Following our efforts toward the synthesis of

Scheme 1. Retrosynthetic Analysis of Dolabelide A

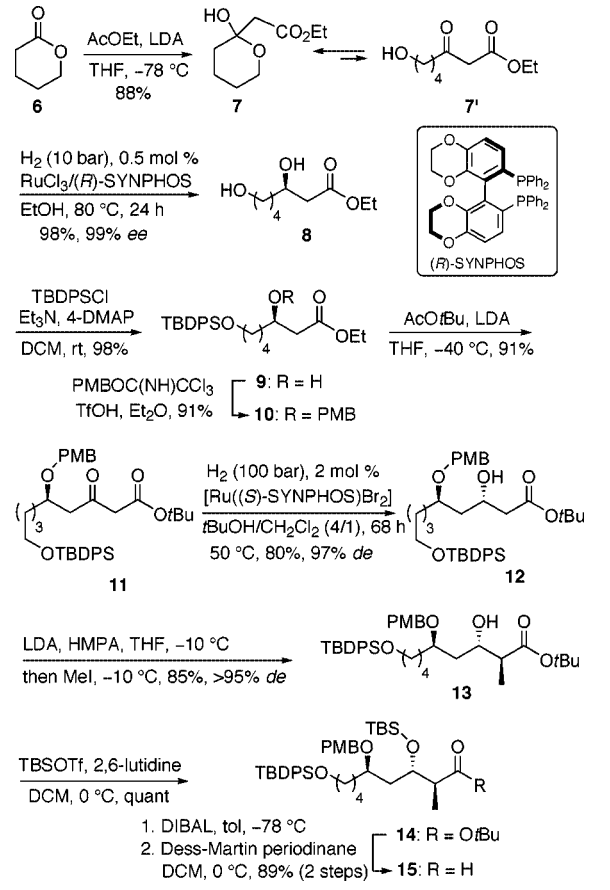


dolabelide A,[4] we report herein the highly stereoselective convergent synthesis of the C15−C30 subunit of this compound, bearing all suitably protected hydroxyl groups.

In our retrosynthetic plan, three of the five stereocenters of the target subunit would be created via ruthenium-mediated asymmetric hydrogenation[7] of β-keto esters using the atropisomeric ligand SYNPHOS[8] as the chiral diphosphine. The trisubstituted C24−C25 (*E*)-double bond would be obtained through addition of alkyne **3** to aldehyde **2** followed by 1,4-addition of methyl cuprate to the resulting ynone and diastereoselective reduction of the ketone function. Our first synthetic task, therefore, was to prepare a suitable aldehyde fragment.

We chose compound **15** as a target, and this was easily prepared in ten steps from δ-valerolactone **6** (Scheme 2).[9]

Scheme 2. Synthesis of Aldehyde **15**



Addition of lithio ethyl acetate to **6** resulted in the formation of the cyclic hemiketal **7**. This compound is in equilibrium with the β-keto ester **7′** which is suitable for the ruthenium-mediated asymmetric hydrogenation of the ketone function. The reduction was carried out using the convenient procedure developed in our laboratories for the in situ preparation of chiral ruthenium−diphosphine complexes starting directly from $RuCl_3$.[10] Thus, hydrogenation of **7**/**7′** using 0.5 mol % of $RuCl_3$ associated to (*R*)-SYNPHOS as a ligand provided β-hydroxy ester **8** in high yield and with excellent enantioselectivity (99% ee, measured by HPLC analysis). After protection of the diol as TBDPS and PMB ethers using standard conditions, subsequent chain extension with lithio *tert*-butyl acetate[11] delivered the β-keto ester **11** required for

(7) For reviews on Ru-catalyzed asymmetric hydrogenation, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (b) Kitamura, M.; Noyori, R. Hydrogenation and Transfer Hydrogenation. In *Ruthenium in Organic Synthesis*; Murahashi, S.-i., Ed.; Wiley-VCH: Weinheim, 2004; pp 3−52. (c) Genet, J.-P. *Acc. Chem. Res.* **2003**, *36*, 908–918. For references to Noyori reductions with BINAP−ruthenium complexes, see: (d) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth., Coll. Vol. IX* **1998**, 589–596. (e) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858.

(8) For the synthesis of SYNPHOS and comparison with BINAP in asymmetric hydrogenation, see:(a) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Tetrahedron Lett.* **2003**, *44*, 823–826. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931–1941. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process. Res. Dev.* **2003**, *7*, 399–406.

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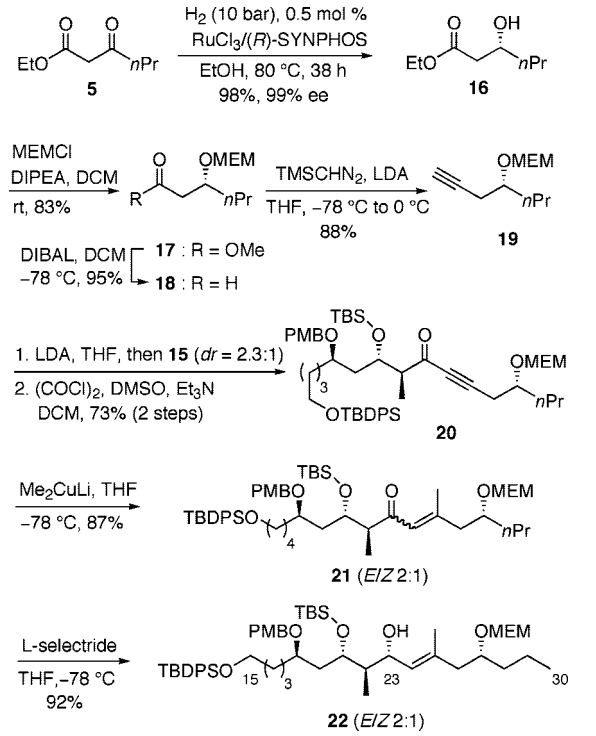
the second hydrogenation reaction. The stereoselective reduction of the ketone was accomplished using the chiral complex [Ru((*S*)-SYNPHOS)Br_2] prepared in situ from commercially available [Ru(COD)(2-methylallyl)$_2$] following the procedure disclosed in our laboratories.[12] The reaction was conducted in a mixture of *tert*-butanol/dichloromethane as the use of methanol as a solvent led to deprotection of the primary alcohol. However the hydrogenation proceeded much slower in the *t*BuOH/CH_2Cl_2 mixture than in MeOH, hence a high pressure of hydrogen (100 bar) and long reaction time (68 h) were required. Under these conditions, the ligand-controlled asymmetric reduction of **11** afforded *β*-hydroxy ester **12** with excellent diastereomeric excess (97% de, determined by HPLC analysis). It was essential to use [Ru(COD)(2-methylallyl)$_2$] as the ruthenium source in this reaction as the use of $RuCl_3$ under the aforementioned optimized conditions failed to afford the expected alcohol in reasonable yield due to low conversion. Subsequent diastereoselective methylation[13] of **12** (>95% de, only one diastereomer detected by ^{1}H NMR) and protection of the alcohol function furnished ester **14** which was finally converted into the corresponding key aldehyde segment **15**. Overall, this sequence allowed the preparation of the C15−C23 fragment of dolabelide A in 42% yield from *δ*-valerolactone **6**.

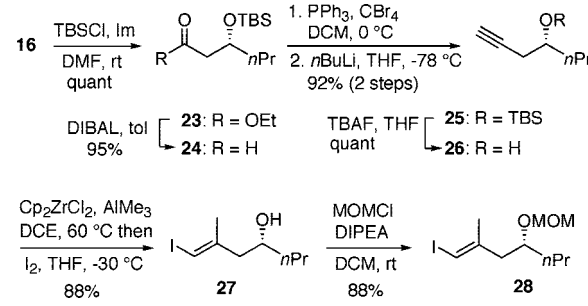
The C24−C30 segment of dolabelide A was readily prepared in four steps from ethyl 3-oxohexanoate **5** as illustrated in Scheme 3. The asymmetric hydrogenation of *β*-keto ester **5** was performed using 0.5 mol % of the $RuCl_3$/(*R*)-SYNPHOS combination and yielded the corresponding alcohol **16** with high enantiomeric purity (99% ee, determined by HPLC analysis). After MEM protection of the alcohol, reduction of **17** into the corresponding aldehyde and exposure of **18** to the Ohira-Shioiri reagent[14] delivered the desired C24−C30 subunit **19**. This sequence proved straightforward, producing **19** in 69% yield for the four steps. Elaboration of the C15−C30 segment consisted then of addition of deprotonated alkyne **19** to aldehyde **15**. The resulting mixture of diastereomeric alcohols was subjected to Swern oxidation to give the corresponding ynone **20**. Subsequent treatment with methyl cuprate then provided enone **21** in good yield albeit with moderate selectivity in favor of the desired (*E*) isomer.

After stereoselective L-selectride reduction of the ketone leading exclusively to the (*R*)-alcohol at C23, the (*Z*) and (*E*) isomers of **22** could be separated at this stage and were isolated, respectively, in 32% and 60% yield, thereby affording an advanced intermediate of the required C15−C30 segment of dolabelide A, lacking only the terminal olefin at C15. However, in view of the moderate selectivity observed in the 1,4-addition of methyl cuprate to **20**, we decided to investigate an alternative approach to the C15−C30 fragment. Therefore, an obvious solution appeared to be replacement of alkyne **19** by a vinyl iodide segment **28** (Scheme 4)

Scheme 3. Synthesis of the C15−C30 Subunit of Dolabelide A (First Approach)



Scheme 4. Preparation of the C24−C30 Segment **28**



whose coupling of the lithiated intermediate with aldehyde **15** would directly afford the desired (*E*)-trisubstituted alkene. While working on this new approach, Hanson and co-workers published the preparation of the C15−C30 fragment of dolabelides based on the same disconnection about the C23−C24 bond, albeit with a shorter aldehyde segment.[3f] In their case, the vinyl iodide was produced from commercially available *R*-(−)-epichlorohydrin, whereas we started from the enantiomerically pure alcohol **16** obtained via asymmetric hydrogenation. The hydroxyl group had first to be temporarily protected as its *tert*-butyldimethylsilyl ether in view of the Corey−Fuchs reaction since attempts to use

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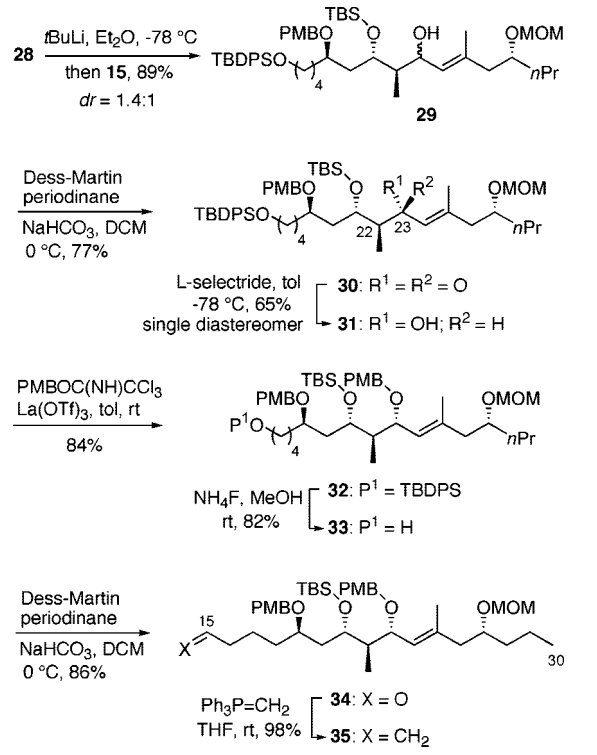
either the free alcohol or the MOM-protected hydroxyl in this reaction failed to afford the corresponding alkyne in reasonable yields (Scheme 4). Exposure of the MOM-protected compound to the Ohira−Shioiri reagent was unsuccessful as well. Thus, after TBS-protection of **16** and reduction of ester **23** into the corresponding aldehyde, alkyne **25** was obtained via a Corey−Fuchs reaction. Subsequent TBS-deprotection followed by zirconocene-promoted carboalumination and quenching with iodine delivered the corresponding vinyl iodide **27** in good overall yield. Finally, MOM-protection furnished the desired C24−C30 fragment. In this new route, a more robust MOM protecting group was used rather than a MEM as in the first approach because the upper fragment of dolabelide A that has been previously synthesized[4b] already contained a MOM ether.

With the new coupling partner **28** in hand, we next completed the construction of the C15−C30 subunit. After metal−halogen exchange (*t*BuLi) followed by addition to aldehyde **15**, a mixture of diastereomeric alcohols **29** (1.4:1) was obtained in 89% yield (Scheme 5). The hydroxyl-bearing C23 stereocenter was nevertheless efficiently set via a Dess−Martin oxidation/L-selectride reduction sequence. Indeed, the reduction proved highly diastereoselective since alcohol **31** was obtained as a single diastereomer following Felkin C22/C23-*anti* selectivity.[15] After protection of the hydroxyl function as a PMB ether,[16] access to compound **35** then required selective removal of the TBDPS group in the presence of a TBS group. To this end, ammonium fluoride in methanol[17] was used and afforded the corresponding alcohol **33** in good yield. Finally, Dess−Martin oxidation led to aldehyde **34** which was immediately subjected to Wittig olefination to furnish the desired C15−C30 subunit of dolabelide A (**35**). Overall, the synthesis of **35** was achieved with a longest linear sequence of 17 steps (11% overall yield) beginning with commercially available δ-valerolactone **6**.

This convergent strategy is based on an iterative process using sequential catalyst-controlled asymmetric hydrogenation reactions of inexpensive prochiral β-keto esters **5** and **7′** and of the readily prepared chiral β-keto ester **11**. Highlights of our synthesis include the efficient use of chiral ruthenium complexes bearing the in-house SYNPHOS ligand and prepared according to procedures developed in our laboratories. All five stereogenic centers of the C15−C30 segment of dolabelide A were set with excellent enantio- or diastereoselectivities (95−99%). Efforts are currently underway to complete the total synthesis of dolabelide A and will be reported in due course.

Scheme 5. Synthesis of the C15−C30 Subunit of Dolabelide A (Second Approach)



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Supporting Information Available: Full experimental procedures and characterization data for all compounds. ^{1}H NMR and ^{13}C NMR spectra for compounds **7**−**15** and **29**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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