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Stereoselective synthesis of C15–C24 and C25–C30 fragments of dolabelides

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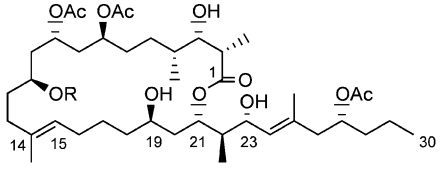
Abstract—The stereocontrolled synthesis of a C15–C24 fragment of dolabelides is reported. The C19 and C21 hydroxyl-bearing stereocenters were installed using ruthenium-mediated asymmetric hydrogenations of cyclic hemiketal **4** and β-keto ester **7**. The C25–C30 portion of dolabelides was prepared as well by ring opening of chiral epoxy alcohol **12** to set up the C27 stereogenic center.

Dolabelide A, a new 22-membered macrolide, and its deacetyl derivative, dolabelide B, were isolated from the Japanese sea hare *Dolabella auricularia* and their structures elucidated in 1995.[1]

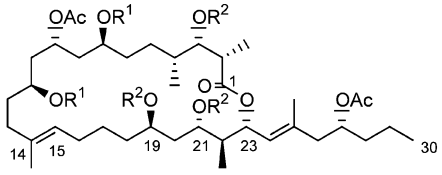
Two 24-membered analogs of these compounds, dolabelides C and D were also isolated in 1997 from the same marine source (Scheme 1).[2]

These macrolides exhibit cytotoxicity against HeLa-S_3 cells with IC_{50} values of 6.3, 1.3, 1.9 and 1.5 μg/mL, respectively. Their structures include eleven stereogenic centers, essentially hydroxyl or derivated functions.

As part of our ongoing program on the use of ruthenium-mediated asymmetric hydrogenation for the preparation of biologically relevant natural products[3–5] as well as of our biocatalytic approach to the synthesis of skipped polyols,[6,7] we decided to undertake the synthesis of these macrolides. Using a logical skeletal disconnection, dolabelides were divided into two fragments corresponding to C1–C14 and C15–C30 of the natural products (Scheme 2). The construction of the C14–C15 junction would be achieved by a Julia one-pot olefination between an aldehyde at C15 and a sulfonyl benzothiazole at C14 or a Wittig reaction between a ketone at C14 and a phosphonium salt at C15. A subsequent macrolactonization reaction between the carboxylic acid at C1 and the appropriate hydroxyl function at either C21 or C23 would then furnish the dolabelide structures. The reverse sequence would also deliver the desired macrocyclic structures. An alternative route would involve a ring closing metathesis between the appropriate alkenes derived from the corresponding alcohols at C14 and C15. The C15–C30 fragment would be obtained via a Horner–Wadsworth–Emmons reaction between β-keto phosphonate **1** and ketone **2** to create the C24–C25 trisubstituted double



dolabelide A R = Ac
dolabelide B R = H



dolabelide C R^1 = Ac, R^2 = H
dolabelide D $R^1 = R^2$ = H

Scheme 1. Structures of dolabelides A, B, C and D.

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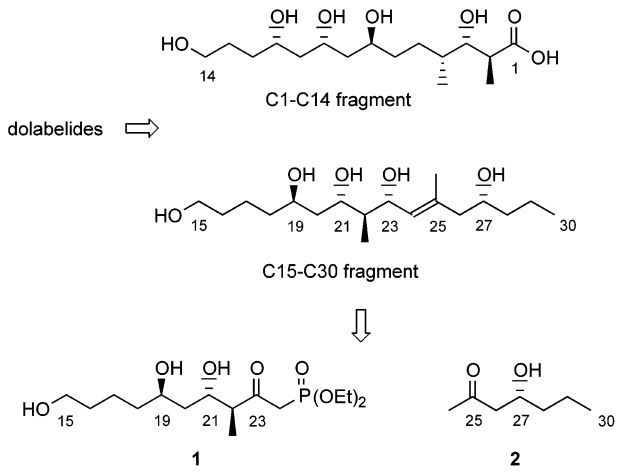


Scheme 2.

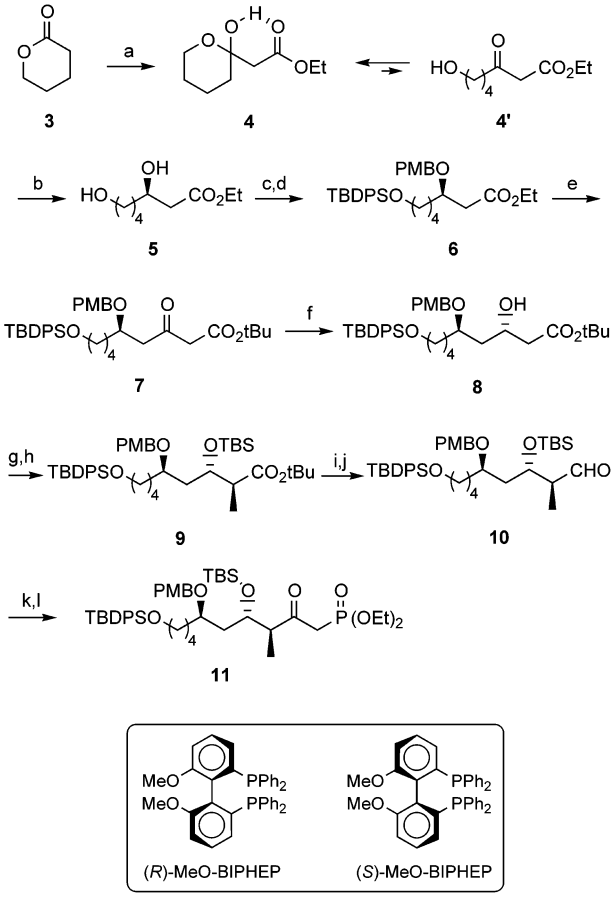
bond, followed by stereoselective reduction of the ketone function to set the hydroxyl group at C23.

To our knowledge only one preparation of the C16–C24 portion of dolabelides has been reported to date.[8] However, in this synthetic approach, the creation of the C21 and C22 stereogenic centers by homoaldol reaction resulted in a 1:1 mixture of diastereomers which were separated in a subsequent step. We describe herein a highly stereoselective synthesis of a C15–C24 fragment of dolabelides using catalytic asymmetric hydrogenation[9,10] of β-keto esters to install the C19 and C21 hydroxyl-bearing stereocenters. The preparation of the C25–C30 fragment is also reported using ring opening of a chiral epoxy alcohol[11] to deliver the C27 stereocenter.

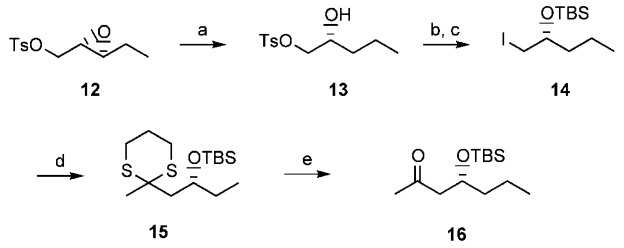
1. Synthesis of the C15–C24 fragment

Synthesis of the C15–C24 subunit started with δ-valerolactone **3** (Scheme 3). Addition of one equivalent of lithio ethyl acetate to **3** at low temperature resulted in the formation of the cyclic hemiketal **4** in 74% yield.[12,13] This compound is in equilibrium with β-keto ester **4′** which is suitable for ruthenium-mediated asymmetric hydrogenation of the ketone function. For this reaction, we used our recently reported simple procedure for the in situ preparation of chiral ruthenium–diphosphine complexes starting directly from anhydrous $RuCl_3$.[14] Thus hydrogenation of **4** was carried out in ethanol at 80°C and low pressure of hydrogen (10 bar) with 1 mol% of the ruthenium complex using (*R*)-MeO-BIPHEP as the ligand. Under these conditions β-hydroxy ester **5** was obtained in 86% yield and excellent enantiomeric excess (e.e. >95%, determined by ^1H NMR with $Eu(tfc)_3$). To our knowledge, this is the first example of asymmetric hydrogenation of a hemiketal to the corresponding β-hydroxy ester. This methodology should provide a rapid access to variously substituted enantiomerically pure ω,β-dihydroxy esters. Compound **5** was then converted into the protected diol **6** in 80% overall yield and subsequent chain extension with lithio *tert*-butyl acetate[15] furnished β-keto ester **7** required for the second asymmetric hydrogenation reaction. We used the chiral ruthenium complex (*S*)-(MeO-BIPHEP)$RuBr_2$ prepared in situ from commercially available (COD)Ru(2-methylallyl)$_2$.[16,17]

The reaction was carried out in a mixture of *tert*-butanol/dichloromethane (8/2) as we have observed not surprisingly that use of methanol as the solvent led to deprotection of the primary alcohol. However the hydrogenation proceeded much slower in the *tert*-butanol/dichloromethane mixture than in methanol, hence high pressure of hydrogen (100 bar) and long reaction time (68 h) were required. Under these conditions, the ligand-controlled asymmetric reduction of **7** provided β-hydroxy ester **8** in 80% yield and excellent diastereomeric excess (d.e. = 96%, determined by HPLC



Scheme 3. *Reagents and conditions*: (a) AcOEt, LDA, THF, −78°C, 2 h, 74%; (b) $RuCl_3$ (1 mol%), (*R*)-MeO-BIPHEP (1 mol%), EtOH, H_2 (10 bar), 80°C, 25 h, 86%, e.e. >95%; (c) TBDPSCl, NEt_3, 4-DMAP cat., CH_2Cl_2, rt, 20 h, 98%; (d) $PMBOC(NH)CCl_3$, CSA cat., CH_2Cl_2, rt, 82%; (e) AcOtBu, LDA, THF, −65 to −30°C, 5 h, 91%; (f) (*S*)-(MeO-BIPHEP)$RuBr_2$ (2 mol%), *t*-BuOH/CH_2Cl_2 (4/1), H_2 (100 bar), 50°C, 68 h, 80%, d.e. = 96%; (g) LDA, MeI, HMPA, THF, −55°C to rt, 3.5 h, 74%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −20°C, 97%; (i) DIBAL, toluene, −78°C, 3.5 h; (j) Dess–Martin periodinane, CH_2Cl_2, 0°C to rt, 4 h, 72% from **9**; (k) *n*-BuLi, diethyl methylphosphonate, THF, −78°C, 2.5 h, 69%; (l) PDC, 4 Å molecular sieves, DMF, rt, 3 h, 86%.



Scheme 4. *Reagents and conditions*: (a) (i) MgI_2, toluene, −60°C, 1 h; (ii) Bu_3SnH, AIBN, toluene, reflux, 1 h, 80%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −50°C to rt, 48 h, 90%; (c) NaI, acetone, Δ, 5 days, 95%; (d) 2-methyl-1,3-dithiane, *n*-BuLi, HMPA, −78°C, 10 min, 86%; (e) I_2, $NaHCO_3$, acetone/H_2O, rt, 45 min, 81%.

analysis, Chiralcel OD-H column, hexane/propan-2-ol: 99/1, flow rate: 1 mL/min). Diastereoselective methylation[18,19] of the β-hydroxy ester (d.e. = 98%, determined by HPLC analysis, Chiralcel OD-H column, hexane/propan-2-ol: 99/1, flow rate: 1 mL/min) followed by protection of the alcohol function then afforded **9** in 70% overall yield. This compound was then converted into the corresponding aldehyde **10** via a hydride reduction/Dess–Martin oxidation sequence. Finally, addition of lithio diethyl methyl phosphonate to **10** followed by oxidation of the resulting β-hydroxy phosphonate provided β-keto phosphonate **11**, required for the Horner–Wadsworth–Emmons reaction. Thus, synthesis of C15–C24 fragment of dolabelides was achieved in twelve steps and 11% overall yield with a high level of enantio- and diastereoselectivity in the construction of the C19, C21 and C22 stereocenters.

2. Synthesis of the C25–C30 fragment

We next turned our attention to the preparation of the C25–C30 subunit, starting from the known compound **12**,[20] obtained via Sharpless asymmetric epoxidation[21] of (*E*)-2-penten-1-ol (Scheme 4).

Opening of the oxirane ring with MgI_2 followed by in situ reduction using Bu_3SnH and AIBN[22] furnished alcohol **13** in 80% yield. The hydroxyl function was protected as its *tert*-butyldimethylsilyl ether and the tosylate was converted into the corresponding iodide **14**. Addition of lithio 2-methyl-1,3-dithiane then afforded compound **15** and oxidative cleavage of the dithiane ring using a heterogeneous mixture of I_2, acetone and aqueous $NaHCO_3$[23] provided **16**. Thus, the C25–C30 subunit of dolabelides was synthesized in five steps and 48% overall yield with complete retention of chirality on the C27 stereocenter.

3. HWE reaction between C15–C24 and C25–C30 subunits

Initial attempts to assemble the C15–C24 (**11**) and C25–C30 (**16**) subunits through a Horner–Wadsworth–Emmons[24] reaction were carried out using conventional methods (NaH, THF). However, under these conditions, competing β-elimination in compound **16** leading to 3-hepten-2-one was a major drawback. We are currently trying various conditions suitable for the base-sensitive ketone **16** as well as different protecting groups on the C25–C30 subunit for this HWE reaction.

In summary, a stereoselective synthesis of a C15–C24 fragment of dolabelides was achieved using catalytic asymmetric hydrogenation of β-keto esters to install the hydroxyl groups at C19 and C21 stereocenters. A C25–C30 fragment was also prepared by regioselective ring opening of a chiral epoxy alcohol to set the C27 stereocenter. This flexible approach should allow the preparation of all stereomers in order to synthesize analogs of dolabelides for structure–activity relationship studies. The completion of the synthesis is currently underway in our laboratory and will be reported in due course.

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