First Stereoselective Synthesis of the C(1)-C(13) Fragment of Dolabelides Using Ruthenium-SYNPHOS®-Catalyzed Asymmetric Hydrogenation Reactions

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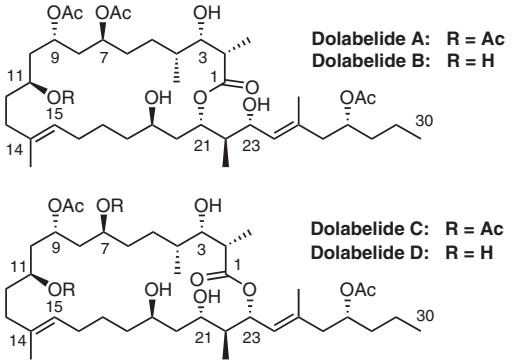
Abstract: The first stereocontrolled synthesis of the C(1)-C(13) fragment of cytotoxic macrolides dolabelides is reported. The C(3), C(7), C(9) and C(11) hydroxyl-bearing stereocenters were installed using ruthenium-mediated asymmetric hydrogenation reactions of the adequate β-keto esters and β-hydroxy ketone.

Key words: asymmetric catalysis, hydrogenation, ruthenium, total synthesis, natural products

Dolabelides A and B were isolated in 1995 from Japanese sea hare *Dolabella auricularia*. Two other similar marine macrolides dolabelides C and D were isolated from the same source in 1997 (Scheme 1).[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. The dolabelides contain a 22- or 24-membered ring, including eleven stereogenic centers. Eight of them are hydroxyl or acetyl functions. Those challenging molecules and especially their *syn*- and *anti*-1,3-diol sequences constitute an excellent target for our ongoing program on the use of ruthenium-mediated asymmetric hydrogenation for the preparation of biologically relevant natural products.[3–5] Moreover, this would allow us to valorize the SYNPHOS® ligand, a chiral atropisomeric diphosphine recently developed by our group.[6]

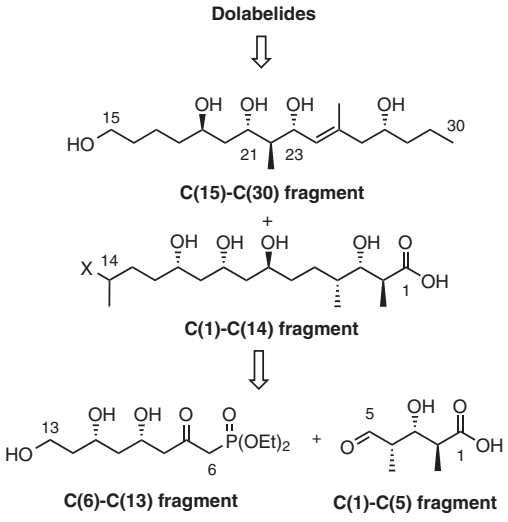
Our retrosynthetic analysis is based on a logical disconnection of dolabelides into two fragments corresponding to C(1)-C(14) and C(15)-C(30) of the natural product (Scheme 2).

The construction of the C(14)-C(15) trisubstituted alkene could be achieved by either a 'one-pot' Julia olefination between an aldehyde at C(15) and a sulfonyl benzothiazole at C(14) or a Horner–Wadsworth–Emmons reaction between an aldehyde at C(15) and a phosphonate at C(14). A subsequent macrolactonization reaction between the carboxylic acid at C(1) and the appropriate hydroxyl function either at C(21) or C(23) would then furnish the dolabelide skeletons. The reverse sequence would also deliver the desired macrocyclic structures.



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

The C(1)-C(14) fragment would result from a Horner–Wadsworth–Emmons reaction between a β-keto phosphonate [C(6)-C(13) fragment] and an aldehyde [C(1)-C(5) fragment] to create the C(5)-C(6) bond. A homologation reaction at the C(13) carbon would then deliver either the sulfonyl benzothiazole or the phosphonate at C(14).



Scheme 2 Retrosynthetic analysis of dolabelides. X = phosphonate or sulfonyl benzothiazole function.

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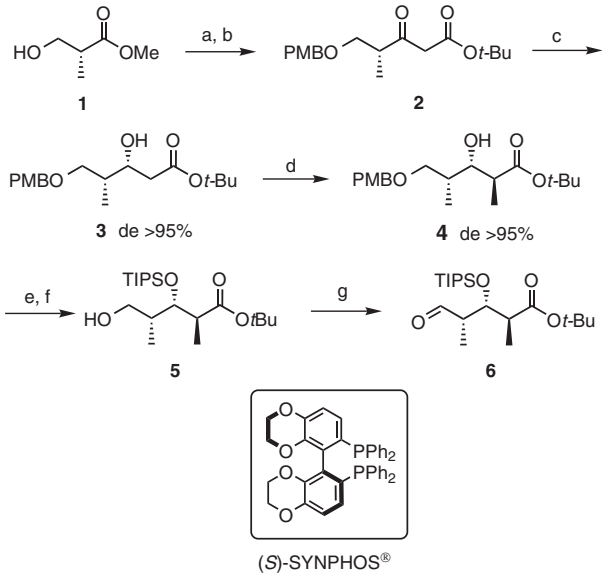
To our knowledge, although one synthetic approach of the C(16)-C(24) fragment of dolabelides[7] and two synthetic approaches of the C(15)-C(30) fragment[8,9] have been described, including one from our group, no synthesis of the C(1)-C(14) portion of dolabelides has been reported so far. We describe herein a highly stereoselective synthesis of the C(1)-C(13) fragment of dolabelides using catalytic asymmetric hydrogenation[10,11] of β-keto esters and β-hydroxy ketone as a key step to install the C(3), C(7), C(9) and C(11) hydroxyl-bearing stereocenters iteratively.

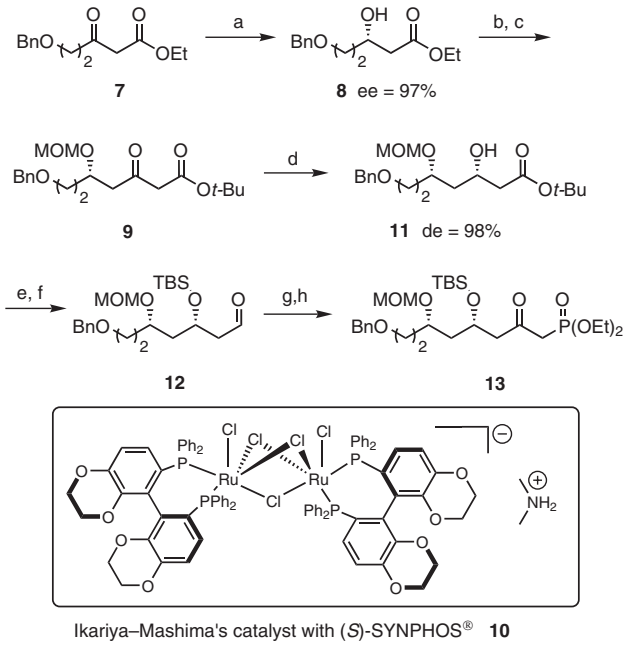
The commercially available Roche ester **1** was used as starting material for the synthesis of the C(1)-C(5) portion which provided in two steps the β-keto ester **2** required for the asymmetric hydrogenation reaction (Scheme 3). Protection of **1** with *p*-methoxybenzyl trichloroacetimidate[12] followed by subsequent side chain extension with lithio *tert*-butyl acetate[13] afforded the desired compound **2** in 64% overall yield. Asymmetric hydrogenation of **2** was performed using the chiral ruthenium complex {Ru[(*S*)-SYNPHOS]Br_2}[6] prepared in situ from commercially available (COD)Ru(2-methylallyl)$_2$.[14,15] The reaction proceeded in 94% yield and with excellent diastereoselectivity (de >95%, determined by ^{1}H NMR), affording β-hydroxy ester **3**. Diastereoselective methylation[16,17] of **3** delivered compound **4** in 72% yield (de >95%, determined by ^{1}H NMR). Conversion of the primary alcohol into the corresponding aldehyde was then achieved smoothly using the following sequence: protection of the secondary alcohol with triisopropylsilyl triflate followed by deprotection of the primary alcohol with DDQ and oxidation of the resulting hydroxy ester **5** with Dess–Martin periodinane furnished **6** in 76% overall yield.



Scheme 3 Synthesis of the C(1)-C(5) fragment. *Reagents and conditions*: a) PMBOC(NH)CCl_3, CSA, CH_2Cl_2, r.t., 24 h, 75%; b) LDA, *t*-BuOAc, THF, –40 °C, 3 h, 85%; c) {Ru[(*S*)-SYNPHOS]Br_2} (2 mol%), H_2 (75 bar), *t*-BuOH–MeOH (4:1), 50 °C, 23 h, 94% (de >95%); d) (i) LDA, THF, –40 °C; (ii) HMPA, MeI, THF, –40 °C to –10 °C, 6 h, 72% (de >95%); e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, –15 °C, 2.5 h, 92%; f) DDQ, CH_2Cl_2, H_2O, 0 °C to r.t., 1 h, 85%; g) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 4.5 h, 97%.

The C(1)-C(5) fragment **6** was thus synthesized in seven steps from **1** in 33% overall yield with excellent diasteroselectivity in the construction of the C(2) and C(3) stereocenters.

The synthesis of the C(6)-C(13) subunit started with β-keto ester **7** required for the first asymmetric hydrogenation reaction (Scheme 4). This compound is readily available from propan-1,3-diol in 3 steps.[18,19] For the asymmetric hydrogenation, we used again the chiral ruthenium complex {Ru[(*S*)-SYNPHOS]Br_2}. The reaction was carried out in ethanol at 80 °C under a low pressure of hydrogen (11 bar) with 1 mol% of ruthenium complex. Under these conditions β-hydroxy ester **8** was obtained in 82% yield and with excellent enantiomeric excess (ee = 97%, determined by HPLC analysis, Chiralcel OD-H column, hexane–propan-2-ol = 90:10, flow rate: 0.8 mL/min).



Scheme 4 Synthesis of the C(6)-C(13) subunit. *Reagents and conditions*: a) {Ru[(*S*)-SYNPHOS]Br_2} (1 mol%), H_2 (11 bar), EtOH, 80 °C, 14 h, 82% (ee = 97%); b) $(CH_3O)_2CH_2$, P_2O_5, $CHCl_3$, 0 °C, 15 min, 86%; c) LDA, *t*-BuOAc, THF, –40 °C, 4.5 h, 84%; d) **10** (2.2 mol%), H_2 (80 bar), MeOH, r.t., 8 h, 93%, (de = 98%); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, –30 °C, 30 min, 92%; f) DIBALH, toluene, –78 °C, 25 min, 85%; g) *n*-BuLi, MeP(O)$(OEt)_2$, THF, –78 °C, 25 min, 87%; h) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 2.5 h, 91%.

Compound **8** was then converted into the MOM protected β-hydroxy ester and subsequent side chain extension with lithio *tert*-butyl acetate[12] furnished β-keto ester **9** in 72% overall yield. This compound was suitable for ruthenium-mediated asymmetric hydrogenation of the ketone function to install the second stereogenic center of the fragment.

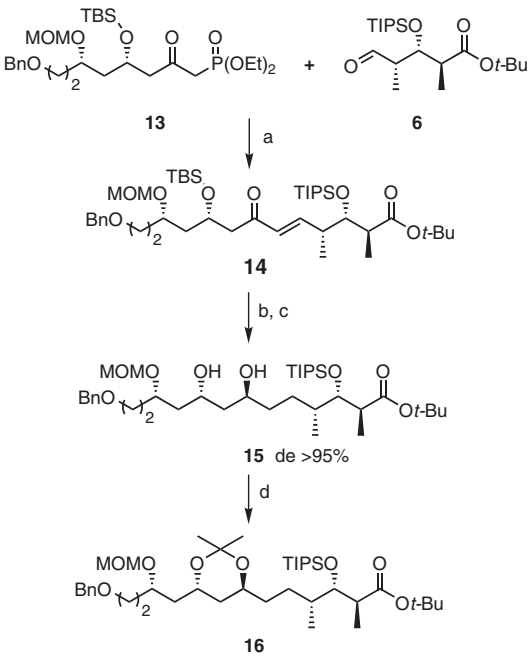
As the use of chiral ruthenium complex {Ru[(*S*)-SYNPHOS]Br_2} resulted in deprotection of the MOM protecting group, we envisaged to employ Ikariya–Mashima's catalyst which is more suitable for acid-sensitive compounds. This catalyst was first synthesized with the chiral diphosphine BINAP by Ikariya and Saburi in 1985.[20] Mashima afterwards correctly described this catalyst using *p*-MeO-BINAP as the chiral diphosphine.[21] The (*S*)-SYNPHOS complex **10** was synthesized in our laboratory using the new and efficient procedure published in 2000 by Mashima et al.[22] Thus, the reaction was carried out with 2.2 mol% of catalyst **10**[23] in methanol at room temperature and under a high pressure of hydrogen (80 bar).[24] Under these conditions, *syn*-β,δ-dihydroxy ester **11** was obtained in 93% yield with excellent diastereoselectivity (de = 98%, determined by HPLC analysis, Chiralcel OD-H column, hexane–propan-2-ol = 99:1, flow rate: 1.0 mL/min).

Protection of the hydroxyl function followed by hydride reduction of the ester then afforded aldehyde **12** in 79% overall yield. Finally, this compound was converted into the corresponding β-keto phosphonate **13** via addition of lithio diethyl methyl phosphonate followed by oxidation of the resulting β-hydroxy phosphonate. Thus, the synthesis of C(6)-C(13) fragment of dolabelides was achieved in eight steps and 34% overall yield with a high level of enantio- and diastereoselectivity in the iterative construction of the *syn*-1,3-diol moiety.

Once the syntheses of C(1)-C(5) and C(6)-C(13) fragments were achieved, we could address the Horner–Wadsworth–Emmons reaction to create the C(5)-C(6) bond (Scheme 5).

This reaction was carried out under Masamune–Roush conditions,[25] suitable for the base-sensitive aldehyde **6**, and afforded stereoselectively compound (*E*)-**14** in 38% yield (78% yield based on recovered starting material). The TBS protecting group was then removed selectively to furnish in 70% yield the β-hydroxy ketone required for the last asymmetric hydrogenation reaction to simultaneously install the C(7) stereogenic center and reduce the alkene. The reaction was carried out in a mixture of *tert*-butanol–methanol (4:1) at 50 °C and under high pressure of hydrogen (80 bar) with 2 mol% of Ikariya–Mashima's catalyst **10**. Under these conditions, compound **15** was obtained in 79% yield and with excellent diastereomeric excess (de >95%, determined by ^{1}H NMR). Conversion of **15** into the corresponding acetonide **16** then proceeded quantitatively and the ^{13}C NMR analysis of **16** confirmed the *anti*-relationship between the C(7) and C(9) hydroxyl groups.[26]

In conclusion, a stereoselective synthesis of the C(1)-C(13) fragment of dolabelides was performed for the first time using catalytic asymmetric hydrogenation of β-keto esters and β-hydroxy ketone to install the hydroxyl groups at C(3), C(7), C(9) and C(11) stereocenters. This flexible strategy is based on an iterative process: catalyst-controlled asymmetric hydrogenation of a β-keto ester and homologation of the resulting β-hydroxy ester into a new β-keto ester for further hydrogenation. This versatile methodology should allow the preparation of analogues of dolabelides in view of structure–activity relationship studies. The achievement of the total synthesis of dolabelides is currently underway and will be reported in due course.



Scheme 5 Synthesis of the C(1)-C(13) fragment of dolabelides. *Reagents and conditions*: a) LiCl, DIPEA, MeCN, r.t., 26 h, 38%; b) 1% HCl in EtOH, r.t., 3 h, 70%; c) **10** (2 mol%), H_2 (80 bar), *t*-BuOH–MeOH (4:1), 50 °C, 23 h, 79% (de >95%); d) 2,2-dimethoxypropane, PPTS, acetone, r.t., 30 min, quant.

Acknowledgment

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(23) **Typical Procedure for the Synthesis of Ikariya–Mashima's Catalyst with (*S*)-SYNPHOS® 10**.
A mixture of $[RuCl_2(\eta^6\text{-benzene})]_2$ (25 mg, 0.05 mmol), (*S*)-SYNPHOS® (64 mg, 0.1 mmol) and dimethylammonium chloride (8 mg, 0.1 mmol) were introduced in a 50 mL round bottom tube equipped with a magnetic stirring bar and a condenser. The mixture was degassed by three vacuum/argon cycles at r.t. Degassed anhyd THF (6 mL) was added. The orange mixture was refluxed overnight and then cooled to r.t. The solvents were evaporated under vacuum and the brown solid **10** was used as crude catalyst for the hydrogenation reaction without further purification.
Typical Procedure for the Hydrogenation Reaction with Ikariya–Mashima's Catalyst 10.
A solution of β-keto ester **9** (110 mg, 0.30 mmol) in degassed MeOH (2.0 mL) was added to Ikariya–Mashima's catalyst **10** (6.0 mg, 0.004 mmol) in a round bottom tube via cannula. The reaction vessel was placed in a stainless steel autoclave, which was purged with hydrogen and pressurized to 80 bar. After stirring for 8 h at r.t., hydrogen was vented and the reaction mixture was concentrated in vacuo. The residue was purified by flash chromatography (C_6H_{12}–EtOAc = 8.5:1.5) to give **11** (102 mg, 0.28 mmol, 93%, de = 98%) as a pale yellow oil.
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