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# Directed Hydrogenations and an Ireland–Claisen Rearrangement Linked to Evans–Tishchenko Chemistry: The Highly Efficient Total Synthesis of the Marine Cyclodepsipeptide Doliculide

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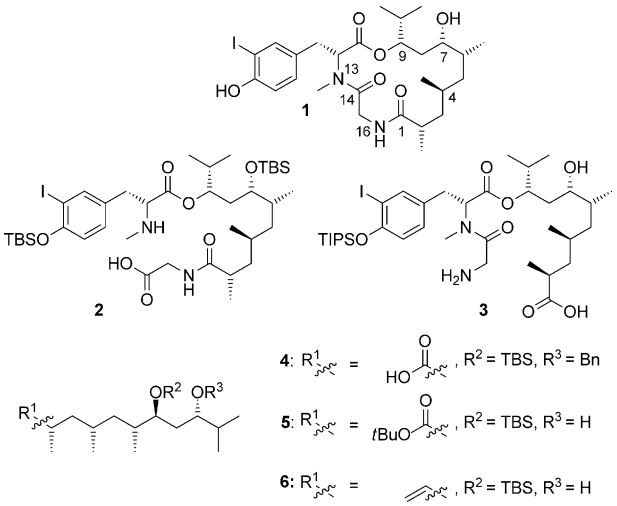
**Abstract:** Two new convergent total syntheses have been developed for the cytotoxic, actin microfilament-stabilizing marine cyclodepsipeptide doliculide (**1**). A key strategic element of both routes is the establishment of the central stereogenic center of the characteristic polydeoxypropionate stereotriad by means of a hydroxyl-directed catalytic hydrogenation of a trisubstituted double bond. The requisite olefin substrates were obtained through a modified Suzuki–Miyaura coupling or through Ireland–Claisen rearrangement of a propionate ester, respectively; the latter was the direct result of a highly selective Evans–Tishchenko reduction of a hydroxy ketone that had been obtained in a stereoselective Paterson aldol reaction. Doliculide (**1**) was finally obtained in a total number of 17 or 15 (14) linear steps, respectively, which represents a substantial improvement over previous syntheses of this highly bioactive natural product.

Natural products perturbing the structure and function of the actin cytoskeleton are powerful molecular tools for the dissection of actin-dependent cellular processes.[1–3] Due to their pronounced antiproliferative activity, they could also serve as lead structures for anticancer drug discovery,[3–5] although the true potential of actin as a viable drug target still remains to be established. Actin-interacting natural products have been isolated from a variety of biological sources, including terrestrial (plants, fungi, bacteria),[6–8] as well as marine (nudibranchs, sponges, algae) organisms,[1] and they cover a diverse range of molecular architectures. Although the oldest actin-interacting natural product, phalloidin,[9,10] is a bicyclic peptide, the majority of currently known natural actin binders feature (mono)macrocyclic core structures of varying ring size and complexity.[11,12] This group also includes the cyclic depsipeptide doliculide (**1**), which was isolated from the sea hare *Dolabella auricularia* by Yamada and co-workers in 1994.[13]




Doliculide (**1**) showed potent in vitro antiproliferative activity against the human leukemia cell line HeLa-S3[13] (with an half maximal inhibitory concentration ($IC_{50}$) value of 1.5 nM) and was later demonstrated to destroy actin stress fibers in cells and to induce actin assembly into clump-like aggregates;[14] the cellular effects of **1** were virtually identical with those of jasplakinolide, a different microfilament-stabilizing cyclodepsipeptide of marine origin that has found widespread use as a tool compound in cell biology.[15]

More recently, **1** was also shown to cause rapid immobilization of G-actin and to induce apoptosis in cancer cells.[16] In spite of its very favorable biochemical and cellular properties, however, doliculide (**1**) has been studied much less extensively than jasplakinolide, including the exploration of structure–activity relationships (SAR).

To date, four successful total syntheses of doliculide (**1**) have been reported in the literature[13,17–20] that are all based on ring closure by macrolactamization, either between C14 and N13[13,17] or between C1 and N16.[18–20] The requisite ω-amino acids **2** or **3** have been elaborated from different C1–C9 precursors (doliculide numbering), including acid **4** (→**2**),[13,17] ester **5** (→**3**),[18,20] and terminal olefin **6** (→**3**).[19] The major conceptual differences between the existing syntheses of doliculide (**1**) relate to the construction of the respective C1–C9 polyketide fragment, with its challenging all-*syn* 1,3,5-trimethyl

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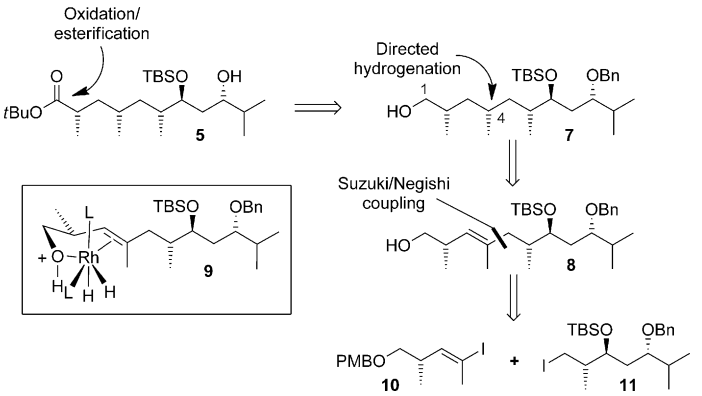
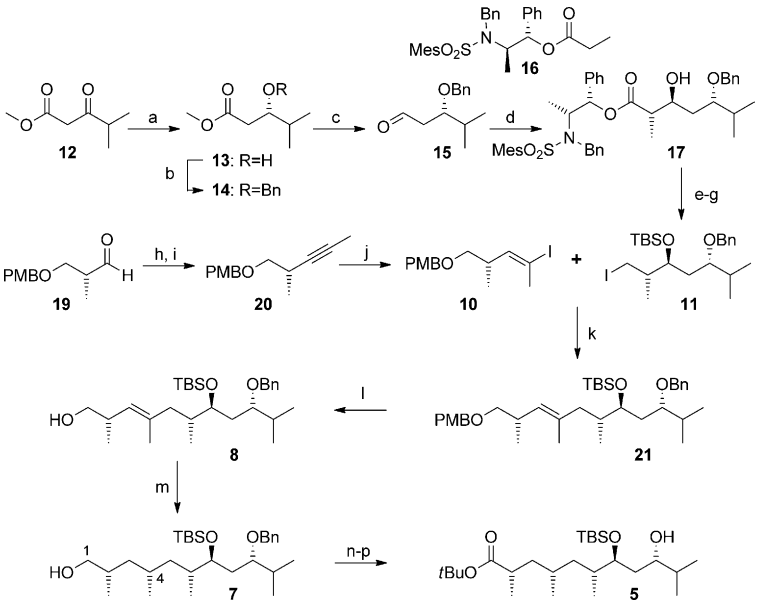
motif; even in the best case, however, 22 linear steps were required to access the respective variant of this key intermediate from readily available starting materials. Herein, we now describe two new approaches to polyketide fragment **5** that are both significantly more efficient than the existing syntheses. The common conceptual feature for both approaches is the establishment of the methyl-containing stereogenic center at C4 by the hydroxyl-directed stereoselective hydrogenation of a trisubstituted double bond.[21] For the shorter of the two routes, this ultimately enabled access to **5** in only 11 or 12 steps (see below) and with almost perfect atom economy.[22,23]

As illustrated in Scheme 1, one possible option to exploit the directing effect of a free hydroxyl group for the establishment of the C4 stereocenter is the change of the oxidation state of C1, thus revealing homoallylic alcohol **8** as a suitable hydrogenation substrate. Based on the conformational model proposed by Evans for the rhodium-catalyzed hydrogenation of trisubstituted olefins related to **8**,[21] the desired isomer **7** was expected to be formed in this reaction with high selectivity (via intermediate **9**, Scheme 1). Alcohol **7** would then be converted into **5** by oxidation of C1 and protection (C1-carboxyl group)/deprotection (C9-hydroxyl group), whereas **8** itself was envisioned to be obtained by Negishi- or Suzuki-type cross-coupling of vinyl iodide **10** and alkyl iodide **11**. The convergent construction of the C1–C9 segment of doliculide (**1**) by the coupling of two fragments of comparable complexity is not part of any of the previous syntheses of the compound; in all four cases, intermediates **4**, **5**, or **6** were obtained by stepwise linear chain extensions.




**Scheme 1.** Retrosynthesis of polyketide fragment **5**. First-generation approach. Bn = benzyl, PMB = p-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.




**Scheme 2.** a) $H_2$ (9 bar), (*R*)-$Ru^{II}Cl_2$[BINAP], MeOH, 100 °C, 6 h, 94%, 93% *ee*; b) benzyl 2,2,2-trichloroacetimidate, TFMSA, $CH_2Cl_2$/cyclohexane 1:2, RT, 20 h, 93%; c) DIBALH, $CH_2Cl_2$, −78 °C, 3 h, 79%; d) **16**, $Et_3N$, *c*-$Hex_2BOTf$, −78 °C, 7 h, 83% (d.r. > 11:1); e) TBSOTf, 2,6-lutidine, −78 °C→0 °C, 1 h, 97%; f) DIBALH, $CH_2Cl_2$, −78 °C, 3 h, 84%; g) $I_2$, $PPh_3$, imidazole, $Et_2O/CH_3CN$ 4:1, RT, 10 min, 86%; h) $Ph_3P$, $CBr_4$ $CH_2Cl_2$, −10 °C, 30 min, 78%; i) *n*BuLi, MeI, THF, −78 °C→RT, 2.5 h, 85%; j) 1. $(nBu)_3Sn(nBu)CuCNLi_2$, THF, 0 °C, 3 h; 2. $I_2$, $CH_2Cl_2$, 0 °C, 49% over two steps. k) **11**, *t*BuLi, 9-methoxy-BBN, [$PdCl_2$(dppf)], ether/DMF 1:1, −78 °C→RT, 17 h, 83%; l) DDQ, pH 7 buffer, $CH_2Cl_2$, RT, 1 h, 82%; m) $H_2$ (9 bar), Rh[(nbd)dppb]$BF_4$ (20 mol%), $CH_2Cl_2$, RT, 8 h, 86%; n) TEMPO, sodium phosphate buffer (pH 6), 80% $NaClO_2$, NaOCl (cat.), $CH_3CN$, 35 °C, 7 h, 83%; o) $(Boc)_2O$, DMAP, *t*BuOH, 30 °C, 5 h; p) $H_2$ (1 atm), 20% $Pd(OH)_2$/C, 1,4-dioxane, 30 °C, 5 h, 85% over two steps. BINAP = (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, DIBALH = diisobutylaluminium hydride, TFMSA = trifluoromethanesulfonic acid, TBSOTf = TBS trifluoromethanesulfonate, BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenyl-phosphino)ferrocene, DDQ = 2,3-dichlor-5,6-dicyano-1,4-benzoquinone, nbd = norbornadiene, dppb = 1,4-bis(diphenylphosphino)butane, TEMPO = 2,2,6,6-tetramethylpiperidinyloxyl, DMAP = 4-dimethylaminopyridine.

In the forward direction, the synthesis of building block **11** commenced with the Noyori reduction[24] of β-keto ester **12**, which provided β-hydroxy ester **13** in high yield (94%) and with 93% enantiomeric excess (*ee*; Scheme 2).[25] Protection of the hydroxyl group in **13** as a benzyl ether followed by diisobutylaluminium hydride (DIBALH) reduction of the ester moiety then furnished aldehyde **15** in 74% overall yield. Aldehyde **15** underwent smooth aldol reaction with the boron enolate of the propionylated Masamune auxiliary **16**,[26] to give the desired *anti*-aldol product **17** in 83% isolated yield (the diastereomeric ratio (d.r.) for the reaction was > 11:1).[27] Silylation of **17** with TBS trifluoromethanesulfonate (TBSOTf) followed by reductive removal of the auxiliary with DIBALH gave a primary alcohol that was converted into iodide **11** in an Appel reaction (Scheme 2). Building block **11** was obtained in 69% overall yield for the three-step sequence from **17**.

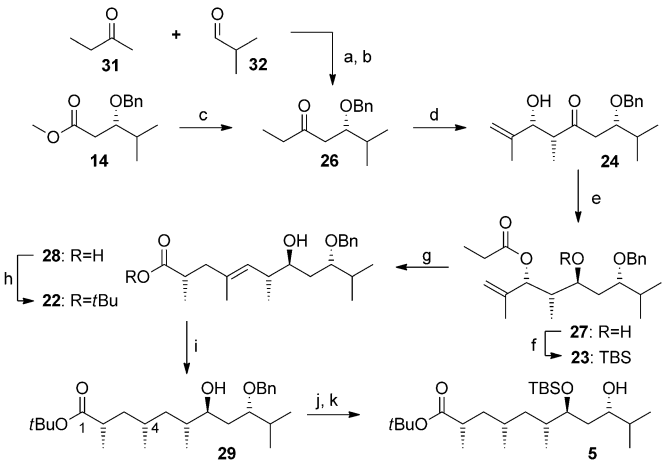
Vinyl iodide **10** was prepared via aldehyde **19** (obtained in two steps from *R*-Roche ester in 94% overall yield), according to procedures previously developed by Smith and co-workers in the context of their synthesis of tedanolide (Scheme 2).[28] Specifically, **19** was converted into alkyne **20** by reaction with $Ph_3P$ and $CBr_4$ to produce a dibromo olefin intermediate, followed by treatment of the latter with *n*BuLi and $CH_3I$. Stannylcupration/iodination of **20** then provided vinyl iodide **10** in 32% overall yield (based on **19**).

The conversion of **11** into a boronate complex by treatment with *n*BuLi and 9-methoxy-BBN and in situ Suzuki coupling of this complex with vinyl iodide **10** gave the desired trisubstituted olefin **21** in excellent yield (83%). Alternatively, **21** could also be obtained from **10** and **11** by Negishi coupling, but the yield of this reaction was substantially lower (51%; for details, see the Supporting Information). Cleavage of the PMB ether in **21** with DDQ then provided the free homoallylic alcohol **8** as the projected substrate for the hydroxyl-directed stereoselective hydrogenation step. In the event, treatment of **8** with hydrogen (9 bar) in $CH_2Cl_2$ in the presence of Rh[(nbd)dppb]$BF_4$ gave the desired stereoisomer **7** in excellent yield (86% after purification by flash chromatography) without the need for any optimization of reaction conditions. Alcohol **7** was elaborated into the polyketide fragment **5** by oxidation, esterification with $BOC_2O$/DMAP[18] and debenzylation of the C9 hydroxyl group with $H_2$/20% $Pd(OH)_2$/C at atmospheric pressure. Overall, **5** was obtained from β-keto ester **12** in only 13 linear steps and 20% overall yield.

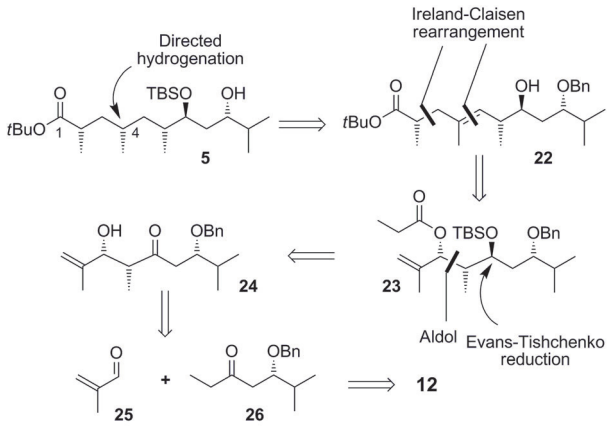
Although the above-described approach delivered the polyketide fragment of doliculide in significantly fewer steps than any of the published syntheses, it appeared that a potentially more effective way of exploiting the directing effect of a homoallylic hydroxyl group in a stereoselective hydrogenation reaction would be the engagement of one of the hydroxyl groups that are integral parts of the doliculide structure. By doing so, the need for a subsequent adjustment of the oxidation state of the hydroxyl-bearing carbon would be eliminated; in addition, the corresponding hydrogenation substrate(s) might be accessible without having to rely on an auxiliary-based anti-aldol reaction to establish the C6 and C7 stereocenters.

When analyzing the different possibilities, the most promising option was found to be the establishment of the C4 stereocenter by exploiting the directing effect of the C7 hydroxyl group in the hydrogenation of olefin **22** (Scheme 3). As for homoallylic alcohol **8**, following the conformational arguments established by Evans,[21] the Rh-catalyzed hydrogenation of **22** was expected to deliver the desired isomer with high selectivity. Protecting-group reshuffling would then lead to **5**. Of the different options evaluated for the construction of **22**, an Ireland–Claisen rearrangement[29,30] of **23** appeared to be particularly attractive, because the latter should be directly accessible via Evans–Tishchenko reduction of hydroxy ketone **24** (Scheme 3);[31] **24** in turn was envisioned to result from the stereoselective aldol reaction between methacrolein (**25**) and ethyl ketone **26**.

As illustrated in Scheme 4, ethyl ketone **26** was readily accessible from ester **14** (which had already been an intermediate in our first generation synthesis; Scheme 2) via formation of the corresponding Weinreb amide and its in situ reaction with ethylmagnesium bromide (Scheme 4).




**Scheme 4.** a) D-proline, DMSO, RT, 48 h, 48%, 80% *ee*; b) benzyl 2,2,2-trichloroacetimidate, TFMSA, $CH_2Cl_2$/cyclohexane 1:2, RT, 18 h, 83%; c) Me(MeO)NH·HCl, EtMgBr, THF, −5 °C→RT, 15 h, 61%; d) (+)-(Ipc)$_2$BOTf, $iPr_2NEt$, $CH_2Cl_2$, −78 °C, 2 h, then methacrolein (**25**), −78 °C, 2 h, −20 °C, 16 h, 63% (brsm 93%, 30% of **26** recovered); e) $SmI_2$, $C_2H_5CHO$, THF, −25→−15 °C, 1 h, 87%; f) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78→0 °C, 30 min, 91%; g) TBSOTf, KHMDS, $Et_2O$, −80→0 °C, 10 h, then HF/$CH_3CN$, 1.5 h, RT, 85%; h) *i*PrNHC(O*t*-$C_4H_9$)=N*i*Pr, *t*BuOH/$CH_2Cl_2$ 1:2, 40 °C, 8 h, 84%; i) $H_2$ (9 bar), Rh[(nbd)dppb]$BF_4$, $CH_2Cl_2$, RT, 8 h, 90%; j) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, −78 °C→0 °C, 1 h; k) $H_2$ (9 bar), 20% $Pd(OH)_2$/C, 1,4-dioxane, RT, 3 h, 86% over two steps. Brsm = based on recovered starting material, (Ipc)$_2$BOTf = diisopinocampheylboron trifluoromethanesulfonate, KHMDS = potassium hexamethyldisilazide.



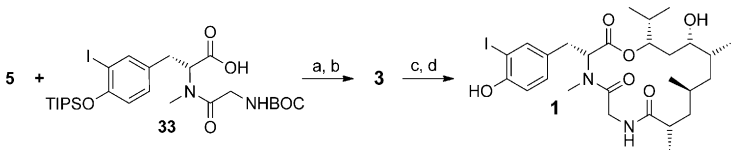

**Scheme 3.** Retrosynthesis of polyketide fragment **5**. Second-generation approach. Bn = benzyl, *t*Bu = *tert*-butyl.

Alternatively, **26** can also be obtained from 2-butanone (**31**) and *iso*-butyraldehyde (**32**) by proline-catalyzed aldol reaction followed by benzylation.[32] However, the *ee* of the organocatalytic aldol reaction did not exceed 80%, and no attempts were made to improve the selectivity of this transformation.[32]

A Paterson aldol reaction between the diisopinocampheyl enolborinate of **26** (obtained by treatment of **26** with freshly prepared diisopinocampheylboron triflate and Hünig base at −78 °C for 2 h) and methacrolein (**25**) gave the desired aldol product **24** as a single isomer in 63% yield.[33] Hydroxy ketone **24** underwent smooth Evans–Tishchenko reduction[31] with propionaldehyde, to give the desired propionate ester **27** in high yield (87%) and with excellent selectivity.[34]

Reaction of **27** with TBSOTf then produced TBS ether **23** as the substrate for the crucial Ireland–Claisen rearrangement. After a series of unsuccessful attempts to induce the rearrangement by treatment with TBSCl/LDA or TMSCl/LDA in

THF/HMPA[29,30] at temperatures between −78 °C and up to 60 °C, the difficulties with the reaction could be overcome by the use of KHMDS and TBSOTf in $Et_2O$/THF.[35] This reagent/solvent combination induced clean rearrangement of **23** and, after the in situ cleavage of the TBS-ester/TBS-ether groups with HF·pyridine, gave acid **28** as a single isomer in a remarkable overall yield of 85%.




**Scheme 5.** a) DCC, DMAP, $CH_2Cl_2$, −20 °C, 25 h, 82%; b) 1. TFA, $CH_2Cl_2$, 0 °C→RT, 3 h; 2. ($NH_3$/MeOH aq.); c) BOP, DMAP, $CH_2Cl_2$, 0 °C→RT, 30 h, 82% over two steps; d) TBAF, THF, 0 °C, 10 min, 84%. DCC = dicyclohexyl carbodiimide, TFA = trifluoroacetic acid, BOP = (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, TBAF = tetrabutylammonium fluoride.

With the critical rearrangement successfully accomplished, esterification of **28** with *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea at 40 °C gave unsaturated ester **22** in 84% yield.[36] The subsequent hydrogenation of **22**, which was to be the second key transformation in our second generation approach to **5**, was conducted under the same conditions that had been successfully employed for the conversion of **8** into **7** (i.e., Rh[(nbd)dppb]$BF_4$, 9 bar $H_2$, $CH_2Cl_2$, RT). Remarkably, the reaction gave the desired product **29** as a single isomer in excellent yield (89%), attesting to the power of the directing effect of the free hydroxyl group; as for the stereoselective reduction of **8**, no further optimization of reaction conditions was required. Ester **29** was then elaborated into **5** by reaction with TBS triflate and subsequent hydrogenolytic removal of the benzyl group in 77% overall yield. The polyketide unit **5** was thus obtained from β-keto ester **12** in only 11 steps and in 15% overall yield (Scheme 2). In principle, the route can be further shortened by one step, if ethyl ketone **26** is produced from 2-butanone (**31**) and *iso*-butyraldehyde (**32**) (see above). Polyketide fragment **5** prepared by either of the two routes described above had identical spectroscopic properties that were also in agreement with the data previously reported for this intermediate in the literature.[18,37]

Polyketide fragment **5** was then elaborated into **1** in 4 steps and 56% overall yield according to Ghosh and Liu (Scheme 5).[18] The analytical data for the material thus obtained were in excellent agreement with those previously reported for the compound in the literature.[17,18] Likewise, the biological profile of synthetic doliculide (**1**)[16] was found to be highly comparable with the one reported for the natural product.[14]

In conclusion, we have developed two new highly efficient, convergent approaches towards the total synthesis of the marine macrolide doliculide (**1**) that are both centered on the establishment of the C4 chiral center by the hydroxyl-directed catalytic hydrogenation of a trisubstituted olefin. While the first generation route, with the directing hydroxyl group at C1, gave **1** in higher overall yield (20% vs. 15%), the second generation approach, which exploited the directing effect of the native C7 hydroxyl group, is shorter (15 (14) linear steps vs. 17 for the first generation approach); the second-generation approach also critically relied on the exploitation of the ester product obtained in an Evans–Tishchenko reduction as a substrate for an Ireland–Claisen rearrangement. To the best of our knowledge, such a strategy is unprecedented in the literature and contributes to the enhanced step economy of our second-generation approach towards doliculide (**1**).

Both syntheses are significantly shorter than any of the previous syntheses of **1**, thus greatly facilitating access to this interesting bioactive natural product. Meanwhile, the chemistry described herein has also been exploited for the synthesis of a series of analogues with modifications in the dipeptide part of **1**. The biological effects of these compounds will be reported in a separate publication.

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**Keywords:** actin · Claisen rearrangement · doliculide · hydrogenation · total synthesis

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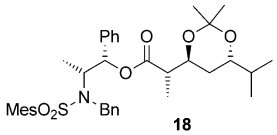



**18**

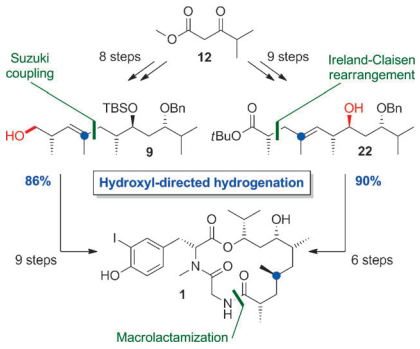
# COMMUNICATION

**Synthetic Methods**

*T. Chen, K.-H. Altmann**

■■ – ■■

**Directed Hydrogenations and an Ireland–Claisen Rearrangement Linked to Evans–Tishchenko Chemistry: The Highly Efficient Total Synthesis of the Marine Cyclodepsipeptide Doliculide**




**Two concise total syntheses** have been developed for the marine natural product doliculide (**1**) from simple β-keto ester **12**. A key strategic element of both syntheses is the high-yielding and highly selective hydroxyl-directed Rh-catalyzed hydrogenation of a homoallylic alcohol intermediate, which was obtained from **12** either by Suzuki coupling (**9**) or Ireland–Claisen rearrangement (**22**) as additional key steps. Both syntheses are substantially shorter than existing routes to **1**.