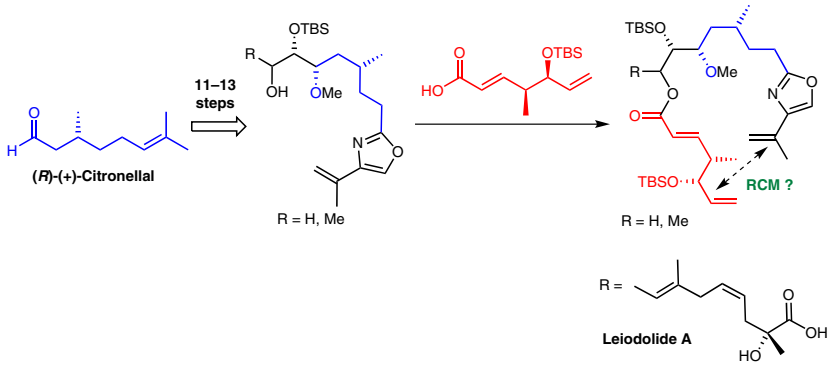
Synlett C. W. Wullschleger et al. Letter

Studies towards the Synthesis of Leiodolide A

Christoph W. Wullschleger
Jun Li[1]
Adriana Edenharter
Karl-Heinz Altmann*

ETH Zürich, Department of Chemistry and Applied Biosciences, Institute of Pharmaceutical Sciences, HCI 405, Vladimir-Prelog-Weg 4, 8093 Zürich, Switzerland
karl-heinz.altmann@pharma.ethz.ch



Received: 24.06.2016
Accepted: 05.08.2016
Published online: 29.08.2016
DOI: 10.1055/s-0036-1588301; Art ID: st-2016-d0408-l

Abstract Two dienes comprising the complete heavy-atom framework of the macrocyclic core of the marine macrolide leiodolide A were prepared by esterification of an appropriate carboxylic acid and two alcohol building blocks. The latter were obtained in a stereoselective fashion from (*R*)-citronellal via a Crimmins-type aldol reaction, oxidative double bond cleavage, and efficient oxazole formation as the key transformations. The possible ring-closing metathesis (RCM) based macrocyclization of the dienes was investigated under different conditions. None of the cyclized product was obtained in any of these experiments, thus indicating that RCM between C6 and C7 may not be a viable strategy for the total synthesis of leiodolide A.

Key words leiodolide, natural product, oxazole, ring-closing metathesis, total synthesis

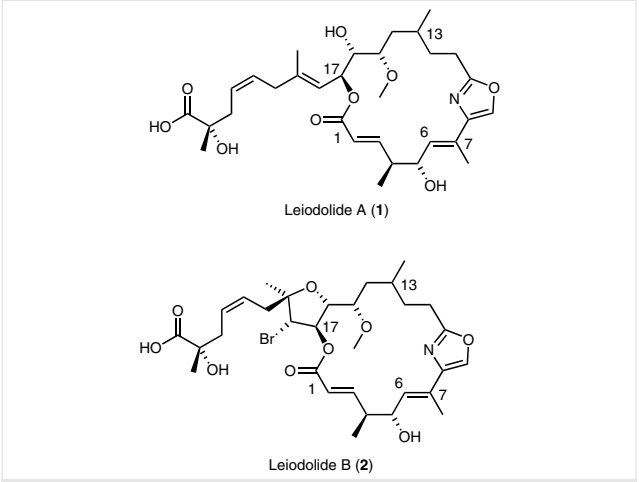


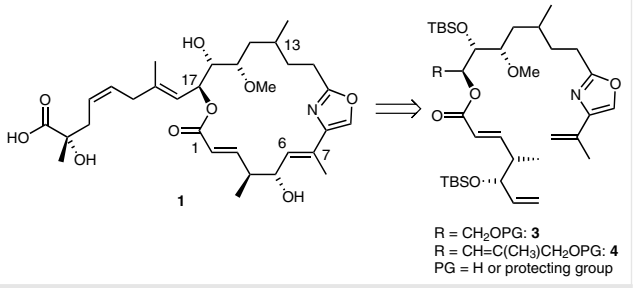
Figure 1 Molecular structures of leiodolides A (**1**) and B (**2**)

Leiodolide A (**1**) is a 19-membered marine macrolide that was isolated in 2006 by Fenical and co-workers from the deep-water marine sponge *Leiodermatium*, together with the related macrolactone leiodolide B (**2**, Figure 1).[2] Leiodolides A/B exhibit several unique structural features, including a conjugated oxazole ring), a carboxylic acid side chain that also incorporates a tertiary alcohol moiety, and in the case of leiodolide B (**2**), a bromine substituent.

Leiodolide A (**1**) has shown significant cytotoxicity in the NCI 60 cell-line panel, with an average GI_{50} of 2.0 μM and sub-μM GI_{50} values against a number of noninterrelated cancer cell lines, including HL-60 (leukemia, 0.26 μM), NCI-H522 (non-small cell lung cancer, 0.26 μM), and OVCAR-3 (ovarian cancer, 0.25 μM).[2] Based on these findings and given our longstanding interest in the chemistry and biology of bioactive natural products,[3] we were attracted to leiodolides as targets for total synthesis and subsequent SAR evaluation. As the configuration of leiodolides had not been fully elucidated by the isolation group (the configuration of the C13 stereocenter remained unassigned), a successful total synthesis would also yield the complete stereochemical assignment of these natural products. The initial focus of our synthetic work was on leiodolide A (**1**) with its somewhat less complex structural framework, which would facilitate analogue synthesis and SAR studies.

Unfortunately, however, synthetic studies by Fürstner and co-workers directed at the total synthesis of leiodolide B (**2**) have shown that its structure had not been assigned correctly by the isolation group (irrespective of the configuration at C13).[4] As none of the possible diastereoisomers of nominal leiodolide B (**2**) prepared in the course of Fürstner's work exhibited spectral properties that were identical with those reported for the natural product, the true structure of leiodolide B (**2**) is currently unknown. These findings also cast doubt on the validity of the structure that has been assigned to leiodolide A (**1**).

In contrast to nominal leiodolide B (**2**), no total synthesis has been disclosed so far for (nominal) leiodolide A (**1**), although a number of reports have described the synthesis of building blocks and advanced intermediates.[5] While all of these efforts were based on the projected construction of the macrocycle by macrolactonization, our own approach towards leiodolide A (**1**) was to entail macrocycle formation by ring-closing olefin metathesis (RCM) between C6 and C7 (Scheme 1).[6]

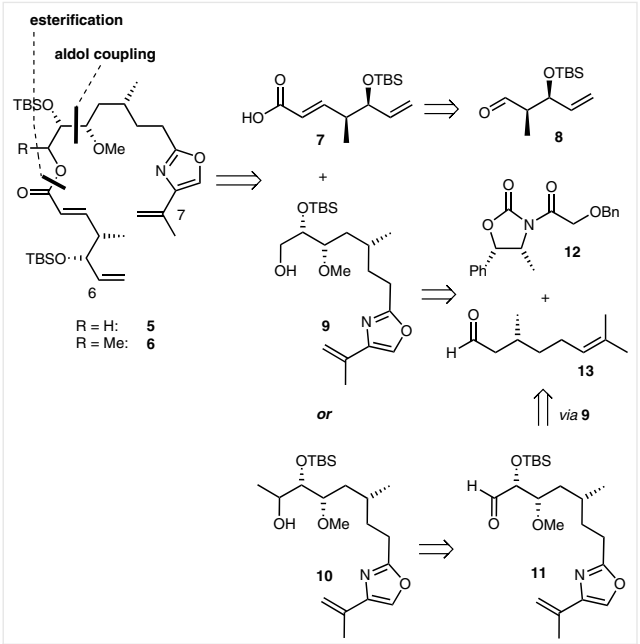


Scheme 1 RCM-based retrosynthesis of leiodolide A (**1**)

As the total synthesis was also meant to set the scene for the subsequent preparation of side-chain-modified variants of **1**, our diene substrate would not incorporate the complete leiodolide A side chain, but rather a less complex, functionalized moiety (as, for example, in dienes **3** or **4**, Scheme 1) that would allow further elaboration into both the natural product as well as side-chain-modified analogues.

We were, however, cognizant of the fact that only a limited number of examples have been described in the literature of RCM-based macrocyclizations involving the formation of a trisubstituted double bond for ring sizes >14.[7] Likewise, we are aware of only one example of an RCM of a diene substrate with one of the reacting double bonds being part of a vinyl oxazole moiety,[8] although in contrast to our case, this double bond was not further substituted (i.e., ring closure led to a disubstituted double bond). Given the scarcity of literature data on related ring-closure reactions, we decided to investigate the inherent feasibility of the projected RCM-based formation of the leiodolide A macrocycle on two model dienes with C17 either unsubstituted (**5**; Scheme 2) or bearing a simple methyl group in place of a functionalized side chain precursor (**6**; Scheme 2). The results of these model studies are summarized in this communication.

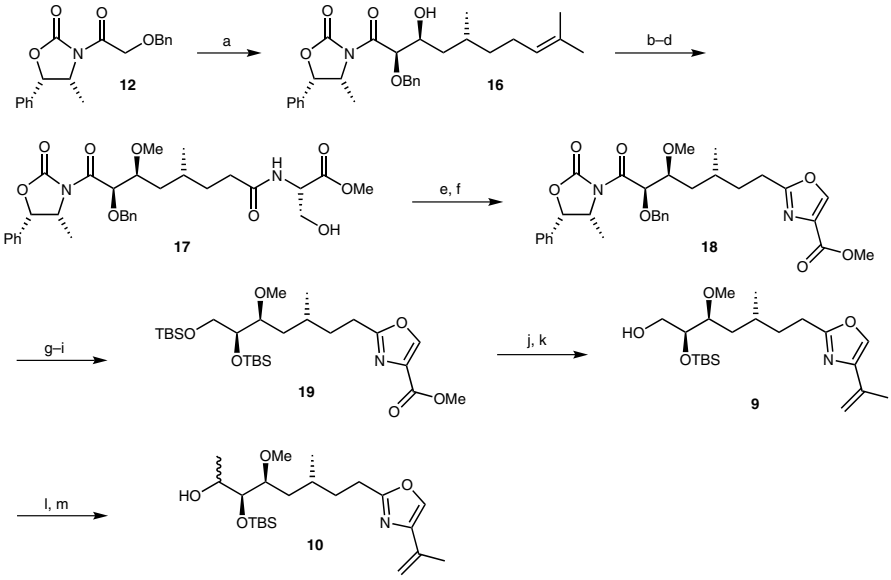
As depicted in Scheme 2, dienes **5** and **6** were to be obtained from acid **7** by esterification with alcohols **9** and **10**, respectively. The latter would in turn be accessed from oxazolidinone **12** and (*R*)-citronellal (**13**) via a Crimmins-type[9] aldol reaction, while acid **7** was to be prepared from aldehyde **8** by Wittig-type chemistry. Importantly at the



Scheme 2 Retrosynthesis of model dienes **5** and **6**

time, this strategy could be readily adapted to the synthesis of dienes **3** or **4**, which would be *en route* to the natural product.

In the forward direction, the aldol reaction of acyl oxazolidinone **12** and (*R*)-citronellal (**13**) under Crimmins conditions ($TiCl_4$, NMP)[9] gave the desired aldol product **16** as a single isomer in 66% yield after chromatographic purification (the reaction produced four diastereoisomers in a 128:12:3:1 ratio)[10] (Scheme 3). In contrast, conducting the reaction under standard Evans aldol conditions with Bu_2BOTf as the Lewis acid gave only incomplete conversion (ca. 55% based on **12**) and a 27% yield of the aldol product. Methylation of **16** with Meerwein salt gave the corresponding methyl ether, which was elaborated into amide **17** by oxidative cleavage of the double bond with $NaIO_4$ in the presence of catalytic amounts of $KMnO_4$[11] and subsequent DCC-mediated coupling of the ensuing carboxylic acid with L-serine methyl ester in high overall yield (43% for the three-step sequence from **16**). It should be noted here that initial attempts at osmium tetroxide promoted catalytic oxidative cleavage of **16** with Oxone® as the stoichiometric oxidant[12] did not yield any of the desired product. In contrast, the use of $NaIO_4$ in combination with catalytic $KMnO_4$ gave the desired carboxylic acid reproducibly in yields of 66–76%. Employing methodology that was developed by Wipf and Williams,[13] amide **17** was then transformed into oxazole **18** by treatment with DAST and subsequent oxidation of the resulting oxazoline with $BrCCl_3$ in 67% overall yield.

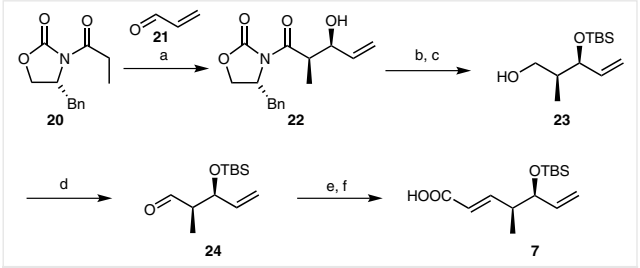


Scheme 3 *Reagents and conditions*: (a) *i*. **12**, $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, NMP, –78 °C, 80 min; *ii*. (*R*)-(+)-citronellal (**13**), –78 °C, 3.5 h, 66%; (b) Me_3OBF_4, Proton Sponge®, CH_2Cl_2, 0 °C, 3 h, 85%; (c) $NaIO_4$, $KMnO_4$ (cat.), K_2CO_3, H_2O–*t*-BuOH–EtOH (4:1:1), r.t., 2.5 h, 66–76%; (d) HCl·H-L-Ser-OMe, DCC, Et_3N, r.t., 75%; e) DAST, CH_2Cl_2, –78 °C, 80 min, 92%; (f) $BrCCl_3$, DBU, CH_2Cl_2, r.t., 19 h, 74%; (g) $NaBH_4$, THF–H_2O (4:1), r.t., 5 h, 71%; (h) Pd/C, H_2, EtOH, r.t., 7.5 h, 72%; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 45 min, 98%; (j) Ph_3PCH_3Br, NaHMDS, Et_2O, r.t., 45 min; then **19** at –78 °C, r.t., 90 min, 78%; (k) $NaIO_4$, THF–H_2O (4:1), r.t., 7 h, 57%; (l) DMP, CH_2Cl_2, 0 °C, 90 min, 58%; (m) MeMgI, THF, –78 °C, 90 min, 50%.

Reductive removal of the oxazolidinone moiety in **18** with $NaBH_4$ in THF–H_2O (4:1)[14] gave the corresponding primary alcohol in good yield (71%); protecting group exchange (Bn → TBS) via catalytic hydrogenation and reaction of the resulting free diol with TBSOTf then furnished bis-TBS ether **19** (70% for two steps). Treatment of **19** with an excess of Ph_3PCH_3Br and NaHMDS resulted in the direct smooth conversion of the methyl ester moiety into an isopropenyl group.[15] Subsequent selective cleavage of the primary TBS ether with $NaIO_4$[16] then gave the free alcohol **9**; oxidation of **9** with DMP followed by reaction of the resulting aldehyde with MeMgBr furnished secondary alcohol **10** as a 6:4 mixture of diastereoisomers at C17 (leiodolide numbering) in 29% yield (based on **9**).

It had been our original plan to retain both the chiral auxiliary as well as the benzyl ether protecting group until after the installment of the isopropenyl moiety on the oxazole ring, but this approach was thwarted by the fact that imide **18**, in contrast to TBS ether **19** could not be converted into the corresponding isopropenyl derivative. While no conversion was observed with eight equivalents of Ph_3PCH_3Br/NaHMDS (the stoichiometry used with **19**), decomposition was induced by increasing the excess of the Wittig reagent, presumably due to opening of the oxazolidinone ring.

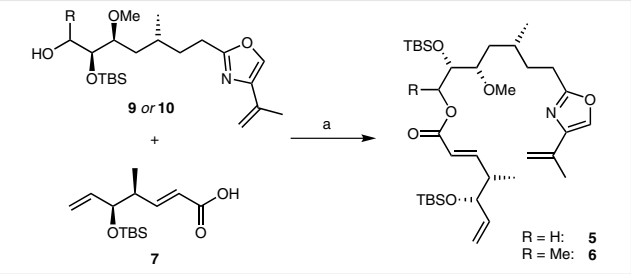
The synthesis of acid **7** is summarized in Scheme 4 and commenced with the aldol reaction of the propionyl-oxazolidinone **20** and acrolein (**21**), which produced the desired *syn*-aldol product **22** in a moderate yield of 51% (single isomer).[17]



Scheme 4 *Reagents and conditions*: (a) *n*-Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, –78 °C to 0 °C, 4 h, 51%; (b) TBSCl, ImH, DMAP, CH_2Cl_2, r.t., 2h, 97%; (c) $NaBH_4$, THF–H_2O, r.t., 22 h, 75%; (d) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 30 min, r.t., 30 min, 81%; (e) $(MeO)_2P(O)CH_2COOMe$, LiCl, DBU, MeCN, r.t., 1 h, 83%; (f) LiOH·H_2O, H_2O_2, THF–H_2O–MeOH (4:1:1), r.t., 10 h, 87%.

Protection of the hydroxy group as a TBS ether followed by reductive removal of the chiral auxiliary with $NaBH_4$ gave monoprotected diol **23**, which was elaborated into acid **7** via aldehyde **24**. The latter underwent a highly stereoselective Horner–Wadsworth–Emmons reaction with methyl dimethylphosphonoacetate under Masamune–Roush conditions;[18] subsequent ester cleavage with LiOOH then gave **7**. Acid **7** was obtained in 43% overall yield for the five-step sequence from aldol product **22**.[19]

The esterification of acid **7** with alcohols **9** or **10** was conducted under Yamaguchi conditions[20] and gave the respective dienes **5** and **6** in moderate yields (42% and 40%, respectively; Scheme 5); no attempts were made to optimize these transformations.[21]



Scheme 5 *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, r.t., 50 min; then DMAP, toluene, r.t., 24 h, **5**: 42%; **6**: 40%.

In a series of preliminary small-scale experiments, dienes **5** and **6** were subjected to different RCM conditions, employing either the Grubbs,[22] Hoveyda–Grubbs,[23] or Piers–Grubbs[24] second-generation catalysts.[25] Unfortunately, none of the desired cyclized product could be detected (TLC, MS) under any of the conditions investigated, mostly due to a lack of conversion.

Obviously, our screening has not been exhaustive and it is conceivable that cyclization might be achievable under conditions other than the ones investigated in this study. Likewise, it cannot be ruled out that the 13*S* isomers of **5** or **6** (leiodolide numbering) could have a higher propensity to undergo the reaction than **5** or **6**. However, notwithstanding these uncertainties, our data indicate that the formation of the leiodolide A macrocycle by means of RCM between C6 and C7 will at least be difficult to achieve.[26] As a consequence, we have redirected our own efforts towards the total synthesis of leiodolide A to a different cyclization approach, but still building on the chemistry that we have developed as part of this study for the synthesis of the C7–C17 segment. This work is currently ongoing and will be reported in due course.

Acknowledgment

This work was supported by the ETH Zürich and by the Swiss Federal Department of Economic Affairs, Education and Research, State Secretariat for Education, Research and Innovation (SERI), as part of COST Action CM0804 ('Chemical Biology with Natural Products') (SERI project C11.0143). We are indebted to Dr. Bernhard Pfeiffer and Leo Betschart for NMR support, and to Dr. Xiangyang Zhang, Louis Bertschi, Rolf Häfliger, and Oswald Greter for HRMS spectra.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588301.

References and Notes

(1) Sandoz GmbH, Biochemiestraße10, 6336 Langkampfen, Austria.
(2) Sandler, J. S.; Colin, P. L.; Kelly, M.; Fenical, W. *J. Org. Chem.* **2006**, *71*, 7245.
(3) For selected recent examples, see: (a) Brütsch, T. M.; Bucher, P.; Altmann, K.-H. *Chem. Eur. J.* **2016**, *22*, 1292. (b) Chen, T.; Altmann, K.-H. *Chem. Eur. J.* **2015**, *21*, 8403. (c) Gaugaz, F. Z.; Redondo-Horcajo, M.; Barasoain, I.; Díaz, J. F.; Cobos-Correa, A.; Kaufmann, M.; Altmann, K.-H. *ChemMedChem* **2014**, *9*, 2227. (d) Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H. *Chem. Eur. J.* **2013**, *19*, 13105. (e) Neuhaus, C.; Liniger, M.; Stieger, M.; Altmann, K.-H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5866. (f) Zurwerra, D.; Glaus, F.; Betschart, L.; Schuster, J.; Gertsch, J.; Ganci, W.; Altmann, K.-H. *Chem. Eur. J.* **2012**, *18*, 16868.
(4) Larivée, A.; Unger, J. B.; Thomas, M.; Wirtz, C.; Dubost, C.; Handa, S.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 304.
(5) (a) Chellat, M. F.; Proust, N.; Lauer, M. G.; Stambuli, J. P. *Org. Lett.* **2011**, *13*, 3246. (b) Zhang, X.; Liu, J.; Sun, X.; Du, Y. *Tetrahedron* **2013**, *69*, 1553. (c) Ren, R.-G.; Li, M.; Si, C.-M.; Mao, Z.-Y.; Wei, B.-G. *Tetrahedron Lett.* **2014**, *55*, 6903. (d) Lee, J.; Panek, J. S. *Tetrahedron Lett.* **2015**, *56*, 6868. (e) Ren, R.; Mao, Z.; Wei, B.; Lin, G. *Chin. J. Org. Chem.* **2015**, *35*, 2313.
(6) For recent reviews on ring-closing olefin metathesis see, e.g.: (a) Schmidt, B.; Hauke, S.; Krehl, S.; Kunz, O. In *Comprehensive Organic Synthesis*; Elsevier: Amsterdam, **2014**, 2nd ed., Vol. 5 1400. (b) van Lierop, N.; Bianca, J.; Lummiss, J. A. M.; Fogg, D. E. In *Olefin Metathesis*; Grela, K., Ed.; John Wiley and Sons: Hoboken, **2014**, 85.
(7) Examples: (a) Sinha, S. C.; Sun, J.; Miller, G. P.; Wartmann, M.; Lerner, R. A. *Chem. Eur. J.* **2001**, *7*, 1691. (b) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796. (c) Trost, B. M.; Dong, G.; Vance, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4540. (d) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585. (e) Tannert, R.; Milroy, L.-G.; Ellinger, B.; Hu, T.-S.; Arndt, H.-D.; Waldmann, H. *J. Am. Chem. Soc.* **2010**, *132*, 3063. (f) Yun, S. Y.; Hansen, E. C.; Volchkov, I.; Cho, E. J.; Lo, W. Y.; Lee, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4261.
(8) Kita, M.; Oka, H.; Usui, A.; Ishitsuka, T.; Mogi, Y.; Watanabe, H.; Tsunoda, M.; Kigoshi, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 14174.
(9) (a) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
(10) **Preparation of Aldol Product 16**
To a cooled (–78 °C) solution of (4*R*,5*S*)-3-(2-(benzyloxy)acetyl)-4-methyl-5-phenyloxazolidin-2-one (3.33 g, 10.2 mmol, 1.00 equiv) in CH_2Cl_2 (100 mL) was added $TiCl_4$ (1.17 mL, 10.7 mmol, 1.05 equiv) dropwise (immediate very intense yellow coloration), and the mixture was stirred for 15 min. Then Hünig's base (99.5%, 1.97 mL, 11.3 mmol, 1.10 equiv) was added dropwise, and the dark-colored solution was stirred for 80 min at –78 °C. After addition of *N*-methyl-2-pyrrolidinone (0.98 mL, 10.2 mmol, 1.00 equiv) at –78 °C, the mixture was stirred for additional 10 min followed by the addition of (*R*)-(+)-citronellal (**13**, 3.70 mL, 20.4 mmol, 2.0 equiv). The dark-colored reaction mixture was stirred for 3.5 h at –78 °C and then allowed to warm to 0 °C over a period of 20 min. The reaction was quenched at 0 °C with 100 mL half-saturated aq NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with sat. aq NaCl (100 mL), then dried over Na_2SO_4, and concentrated to yield a yellow oil. Purification of this material by flash chromatography (hexane–EtOAc, 5:1 → 3:1 → 2:1) afforded the desired aldol product as a viscous, colorless oil (3.24 g, 66%) and a mixture of undesired diastereomers (489 mg, 10%, dr = 12:3:1; ratio of all diastereoisomers formed in the reaction = 128:12:3:1).
R_f = 0.44 (hexane–EtOAc 2:1); R_f = 0.13 (hexane–EtOAc, 5:1); $[\alpha]_D^{23}$ +45.8° (*c* 0.919, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ =

7.45–7.28 (m, 10 H), 5.72 (d, *J* = 7.1 Hz, 1 H), 5.14–5.09 (m, 1 H), 5.11 (d, *J* = 2.3 Hz, 1 H), 4.77 (quint, *J* = 6.8 Hz, 1 H), 4.72 (d, *J* = 11.4 Hz, 1 H), 4.50 (d, *J* = 11.4 Hz, 1 H), 4.09–4.01 (br m, 1 H), 2.16 (br d, *J* = 9.0 Hz, 1 H), 2.06–1.92 (m, 2 H), 1.78 (ddd, *J* = 13.6, 9.9, 4.3 Hz, 1 H), 1.73–1.66 (m, 1 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.41–1.16 (m, 3 H), 0.92 (d, *J* = 6.7 Hz, 3 H), 0.90 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 153.2, 137.2, 133.1, 131.3, 129.0, 128.9 (2 C), 128.6 (2 C), 128.6 (2 C), 128.3, 125.7 (2 C), 124.9, 80.6, 79.9, 73.2, 70.7, 55.5, 41.4, 37.9, 28.9, 25.8, 25.6, 19.1, 17.8, 14.5. IR (film): 3475 (w, br, 3600–3250), 2962 (w), 2925 (w), 1778 (s), 1709 (m), 1455 (m), 1342 (s), 1198 (s), 1147 (m), 1121 (s), 1030 (m). ESI-HRMS: *m/z* calcd for $C_{29}H_{37}NNaO_5$ $[M + Na]^+$: 502.2564; found: 502.2558.

(11) (a) Lemieux, R. U.; von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1701. (b) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.

(12) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc.* **2002**, *124*, 3824.

(13) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(14) Prashad, M.; Her, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.

(15) Uijttewaal, A. P.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1975**, *16*, 1439.

(16) (a) Wang, M.; Li, C.; Yin, D.; Liang, X.-T. *Tetrahedron Lett.* **2002**, *43*, 8727. (b) Li, J.; Menche, D. *Synthesis* **2009**, 1904.

(17) The synthesis of aldol product **22** has been described previously: (a) Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119. (b) Cook, C.; Guinchard, X.; Liron, F.; Roulland, E. *Org. Lett.* **2010**, *12*, 744.

(18) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(19) The TES-protected variant of acid **7** has been prepared by an analogous strategy: Crimmins, M. T.; O'Bryan, E. A. *Org. Lett.* **2010**, *12*, 4416.

(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(21) **Preparation of Ester 5**
To a solution of carboxylic acid **7** (9.30 mg, 0.0344 mmol, 2.14 equiv) and Et_3N (0.011 mL, 0.0764 mmol, 4.75 equiv) in THF (0.5 mL) was added 2,4,6-trichlorobenzoyl chloride (9.0 µL, 0.0573 mmol, 3.56 equiv) dropwise. The reaction mixture was stirred for 50 min, then a solution of alcohol **9** (6.40 mg, 0.0161 mmol, 1.00 equiv) in toluene (0.5 mL) and 4-dimethylaminopyridine (Aldrich 99%, 8.00 mg, 0.0650 mmol, 4.04 equiv) were added; a suspension formed immediately after the addition of DMAP. The resultant white/grey suspension was stirred at r.t. for 24 h, when the reaction was quenched with sat. aq $NaHCO_3$ (3 mL), which was followed by the addition of EtOAc (4 mL). The organic layer was separated and the aqueous solution was extracted with EtOAc (2 × 4 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc–hexane, 1:10) to afford ester **5** as an oil (4.4 mg, 42%).
R_f = 0.31 (hexane–EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 5.78–5.73 (m, 1 H), 5.71 (br t, *J* = 2.7 Hz, 1 H), 5.63 (t, *J* = 7.0, 1 H), 5.25 (dt, *J* = 17.1, 1.8 Hz, 1 H), 5.07 (dt, *J* = 10.4, 1.8 Hz, 1 H), 5.03 (br t, *J* = 1.5 Hz, 1 H), 4.51 (br d, *J* = 4.7 Hz, 1 H), 4.23 (dd, *J* = 10.1, 1.6 Hz, 1 H), 4.09–3.97 (m, 2 H), 3.40 (s, 3 H), 3.26–3.22 (m, 1 H), 3.08 (d, *J* = 7.0 Hz, 1 H), 2.84–2.70 (m, 2 H), 1.99 (br t, *J* = 1.1 Hz, 3 H), 1.84–1.75 (m, 1 H), 1.73–1.60 (m, 2 H), 1.56 (d, *J* = 2.8 Hz, 3 H), 1.44–1.39 (m, 2 H), 1.32–1.26 (m, 1 H), 0.94 (d, *J* = 6.3 Hz, 3 H), 0.893 (s, 9 H), 0.886 (s, 9 H), 0.08 (s, 6 H), 0.04 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 165.2, 160.6, 141.7, 140.0, 133.6, 133.6, 116.9, 114.2, 112.8, 80.7, 78.5, 70.2, 66.1, 58.5, 36.3, 35.1, 33.6, 29.5, 26.1, 26.0 (3 C), 25.9 (3 C), 19.9, 18.9, 18.5, 18.2, 12.0, –4.4, –4.6, –4.7, –4.8.

(22) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(23) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(24) Romero, P. E.; Piers, W. E.; McDonald, R. *Angew. Chem. Int. Ed.* **2004**, *43*, 6161.

(25) Reactions were carried out with 0.5 mg or 1 mg of dienes **5** or **6** at concentrations <0.004 M in DCE or toluene at reflux temperature for several hours. No conversion was observed at r.t. Conversion was assessed by TLC and MS (ESI^+). Diene **5** was only investigated with the Grubbs II and the Hoveyda–Grubbs II catalysts.

(26) While we were primarily interested in the behavior of the O-protected dienes **5** and **6** (in light of the strategy depicted in Scheme 1), we have also prepared small quantities of the free parent compounds by treatment of **5** and **6** with HF-pyridine. In orienting experiments with these materials on an analytical scale we could not detect any cyclized product; in fact, the free alcohols seemed to be highly prone to decomposition under RCM conditions, although definitive conclusions are not possible, due to the small scale of the reactions.