Concise Synthesis of the C3-C14-Fragment of the Antitumor Agent Laulimalide. Application of Jacobsen's HKR Reaction

E. Kate Dorling, Elisabeth Öhler, Andreas Mantoulidis, Johann Mulzer*

Institut für Organische Chemie der Universität Wien, Währinger Strasse 38, A-1090 Wien, Austria

E-mail: johann.mulzer@univie.ac.at

Received 29 March 2001

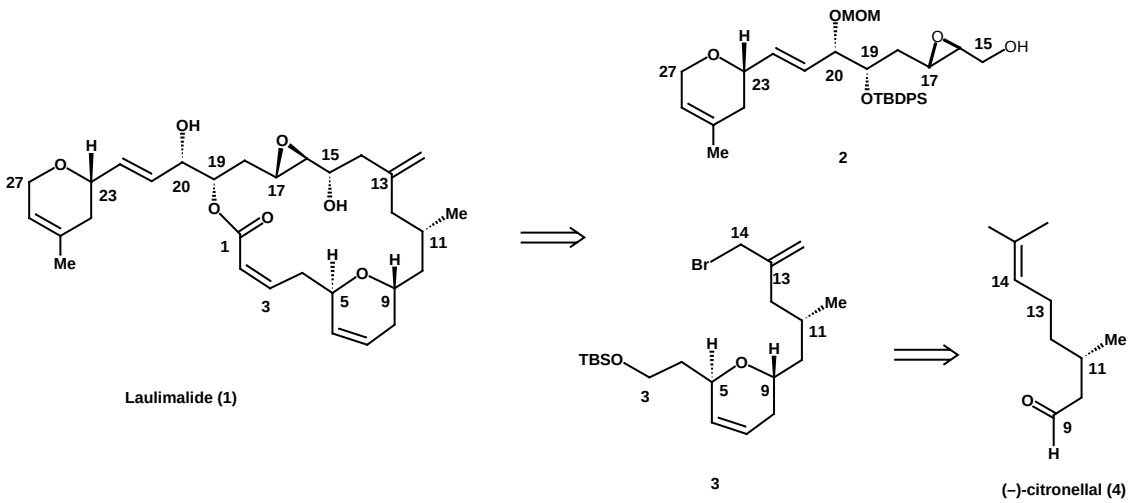
Abstract: Bromide **3**, which represents an appropriately functionalized C3-C14-fragment of the antitumor agent laulimalide (**1**) has been synthesized from (–)-citronellal (**4**) in an overall yield of ca. 17% (12 isolated intermediates). At a very early stage, the synthesis makes use of Jacobsen' s HKR reaction to produce epoxide **8** in diastereomerically pure form.

Key words: antitumor agents, epoxides, Jacobsen's HKR reaction, Eschenmoser methylenation

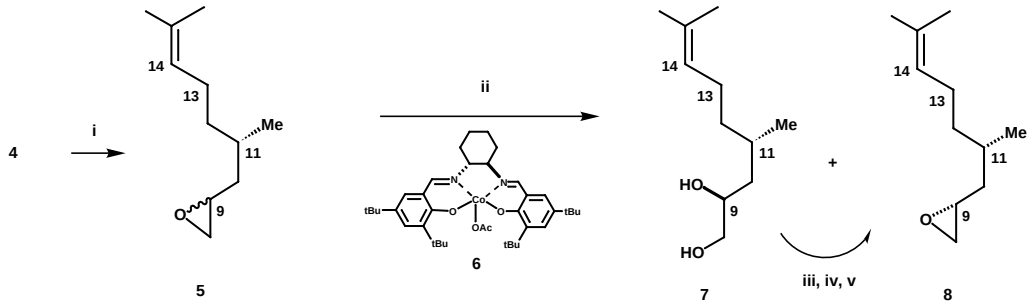
Since the advent of paclitaxel (Taxol)[1] a great deal of effort has been focused on potential successors with the same mode of microtubule stabilizing antitumor action, however with higher activity, in particular against multidrug resistant tumor cells, and better bioavailability. Among recent advances have been epothilone B and derivatives,[2] discodermolide[3] and eleutherobin.[4] Quite recently, it has been discovered that laulimalide (**1**), a metabolite from various marine sponges,[5] also shows microtubule stabilization in eukaryotic cells and is distinguished by an unusually high antitumor activity against multidrug resistant cells lines.[6] These findings have kindled enormous interest in the total synthesis of the compound, and, to date, only one total synthesis of **1** has been published[7] along with several approaches to major fragments.[8] In continuation of our earlier retrosynthetic analysis, which has resulted in an efficient synthesis of the C27-C15 fragment **2**,[8g] we report now an efficient access to allyl bromide **3**, which corresponds to the C3-C14 section of **1** and is to be coupled with the C15 aldehyde derived from **2** by means of a Hiyama Nozaki reaction.[9]

Our plan (Scheme 1) was based on the similarity of **3** with naturally occurring (–)-citronellal (**4**). In particular, the aldehyde function in **4** lent itself to some kind of diastereocontrolled CC connection which eventually should lead to the formation of the dihydropyran ring. Among other options the conversion of the aldehyde into the epoxide[10] appeared attractive which could then be opened by acetylide additions. The epoxide, in turn, should be generated in diastereopure form by Jacobsen's HKR (hydrolytic kinetic resolution).[11] As shown in Scheme 2, aldehyde **4** was converted into a 1:1-mixture of the epoxide diastereomers **5** via Corey's sulfonium ylide addition.[10]

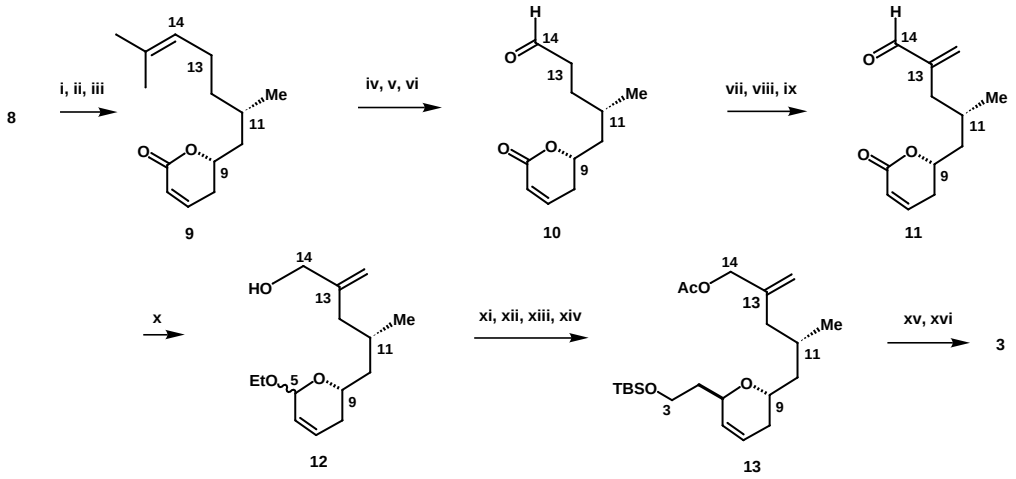
HKR of **5** with catalyst **6**[13] led to the formation of diol **7** along with the desired epoxide **8**, both diastereomerically pure according to standard criteria. Diol **7** was quantitatively transformed into **8** by a dehydrative cyclization under inversion of configuration at C9. In this way, aldehyde **4** was converted into epoxide **8** with an overall yield of 74%. The synthesis was continued by addition of ethyl propiolate anion to C8; Lindlar hydrogenation afforded the (*Z*)-enoate which was cyclized in situ to form lactone **9** in nearly quantitative yield. The differentiation of the two double bonds turned out to be easy by epoxidizing the electron rich olefin selectively with *m*CPBA, opening the



Scheme 1



Scheme 2 Reagents and conditions: i, trimethylsulfonium iodide, KOH, CH_3CN:H_2O (1000:1), 60 °C, 2 h, 95%; ii, catalyst **6** (5 mol%), H_2O (0.5 mol equiv.), TBME, 22 °C, 48 h, 42% of **7**, 41% of **8**; iii, TBDPSCl, imidazole, DMF, 22 °C, 12 h, 94%; iv, MsCl, NEt_3, CH_2Cl_2, 0 °C, 10 min; v, TBAF, THF, 0 °C, 5 min, then 20% NaOH-H_2O, 22 °C, 10 min, 89% over two steps.



Scheme 3 Reagents and conditions. i, ethyl propiolate, *n*BuLi, BF_3-etherate, THF, -95 °C, 2 h, 91%; ii, Lindlar's catalyst, quinoline, H_2, EtOH, 22 °C, 6 h; iii, pTsOH (cat), benzene, reflux, 1 h, 97% over two steps; iv, *m*CPBA, $NaHCO_3$, DCM, 0 °C, 20 min; v, $HClO_4$, H_2O, THF, 22 °C, 1 h; vi, $NaIO_4$, MeOH, H_2O, 22 °C, 3 h, 77% over three steps; vii, $Me_2N = CH_2I$, NEt_3, DCM, 22 °C, 12 h; viii, MeI, Et_2O, $CHCl_3$, 22 °C, 12 h; ix, K_2CO_3, $CHCl_3$, 22 °C, 6 h, 66% over three steps; x, DIBAL, DCM, -78 °C, 1 h, then ethanol, pTsOH, 22 °C, 1 h, 78%; xi, Ac_2O, DMAP, pyridine, 22 °C, 45 min, 93%; xii, vinyloxytrimethylsilane, $LiClO_4$, EtOAc, DCM, 22 °C, 12 h; xiii, $NaBH_4$, MeOH, 0 °C, 30 min, 85% over two steps; xiv, TBSCl, imidazole, DMF, 22 °C, 2 h, 73%; xv, K_2CO_3, MeOH, H_2O, 22 °C, 3 h, 85%; xvi, CBr_4, PPh_3, acetonitrile, 22 °C, 1 h, 65%.

epoxide hydrolytically and cleaving the resulting diol with $NaIO_4$. Without affecting the 6,7-double bond aldehyde **10** was generated which was used for an Eschenmoser methylenation[12] to introduce the exo-methylene group at C13. In fact this operation could be performed in one pot with an overall yield of ca. 70% to furnish olefin **11**. The reaction with DIBAL converted the aldehyde into the allylic alcohol and the lactone into the lactol which was immediately transformed into an anomeric mixture of the 5-ethyl acetals **12**. After acetylation of the 14-alcohol the compound was ready for the introduction of the C2-C3 appendage. Vinyloxytrimethylsilane was added with high diastereoselectivity to the 5-oxonium ion generated from **12** and the resulting C3 aldehyde was reduced to the alcohol with sodium borohydride. TBS protection furnished intermediate **13** which was selectively 14-O-deprotected with potassium carbonate and the alcohol was converted into the desired allylic bromide **3**.

Acknowledgement

Financial support by the Austrian Research Foundation (FWF, project P-13941-CHE) is gratefully acknowledged.

References and Notes

(1) For a review, see: Nicolaou, K.C.; Dai, W.-M.; Guy, *Angew. Chem Int. Ed. Engl.* **1994**, *33*, 15-44.
(2) For a review, see: Nicolaou, K.C.; Roschangar, F.; Vourloumis, D., *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2014-2045.
(3) Gunasekara, S.P.; Gunasekara, M.; Longley, R.E. *J. Org. Chem.* **1990,** *55*, 4912-4915.
(4) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744-8745.

(5) Quinoa, E.; Kakou, Y.; Crews, P. *J. Org. Chem.* **1988**, *53* 3642-3644. Corley, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. *J. Org. Chem.* 1988, *53* 3644-3646. Jefford, C. W.; Bernardinelli, G.; Tanaka, J.-I.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159-162.
(6) Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653-660.
(7) Ghosh, A. K.; Wang, Y. *J. Am. Chem. Soc*. **2000**, *122* 11027-11028. *Tetrahedron Lett.* **2001**, *42*, 3399-3402.
(8) a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1997**, *38* 2427-2430. b) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41* 2319-2322. c) Ghosh, A. K.; Wang, Y. *Tetrahedron Lett.* **2000**, *41* 2319-2322. d) Shimizu, A.; Nishiyama, S. *Tetrahedron Lett.* **1997**, *38* 6011-6014. e) Shimizu, A.; Nishiyama, S. *Synlett* **1998** 1209-1210. f) Mulzer, J.; Hanbauer, M. *Tetrahedron Lett*. **2000**, *41*, 33-36. g) Mulzer, J.; Dorling, E. K.; Öhler, E. *Tetrahedron Lett*. **2000**, *41* 6323-6326. h) Paterson, I.; De Savi, C.; Tudge, M. *Org. Lett*. **2001**, *3*, 213-215. i) Messenger, T.; Davidson, B. S. *Tetrahedron Lett*. **2001**, *42*, 787-800. j) Nadolski, G. T.; Davidson, B. S *Tetrahedron Lett.* 2001, *42*, 801-803.
(9) For reviews, see: Cintas, P. *Synthesis* **1992**, 248-257. Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1-36.
(10) Borredon, E.; Delmas, M.; Gaset, A. *Tetrahedron Lett*. **1982**, *23* 5283-5286.
(11) Jacobsen, E. N.; Hinterding, K. *J. Org. Chem.* **1999**, *64*, 2164-2165. Jacobsen, E. N.; Tokunaga, M.; Larrow, J. F.; Kakiuchi, F. *Science* **1997**, *277*, 936-938. Jacobsen, E. N.; Furrow, M. E.; Schaus, S. E. *J. Org. Chem.* **1998**, *63*, 6776-6777.
(12) Paquette, L.; Dyck, B. P. *J. Am. Chem. Soc.* **1998**, *120*, 5953-5960.
(13) **Procedure for Jacobsen's HKR, preparation of 8.** The Jacobsen (salen)Co(III)(OAc) catalyst **6** (150 mg, 1 mol%) was added to a solution of the epimeric epoxides **5** (3.80 g, 22.6 mmol) in dry TBME (4 mL, resulting in a 5 M solution). The solution was cooled to 0 °C and water (203 μL, 11.3 mmol) was added. The resulting mixture was stirred at 22 °C for 36 h. The reaction mixture was diluted with DCM and filtered though a short pad of celite, washing with DCM. The organic solution was concentrated under reduced pressure and the crude product purified by flash column chromatography, eluting with hexane-ethylacetate (50:1 then 1:2), to yield 1.57 g (42%) of **7** and 1.72 g (41%) of **8** as colorless oils.
(2*R*)-2-[(2*S*)-2,6-dimethylhept-5-enyl]oxirane (**8**):
δ_H (400 MHz, $CDCl_3$) 0.98 (3 H, d, *J* 6.6), 1.21-1.44 (3 H, m), 1.54-1.60 (1 H, m), 1.61 (3 H, s), 1.69 (3 H, d, *J* 1.3), 1.67-1.74 (1 H, m), 2.01 (2 H, m), 2.46 (1 H, dd, *J* 2.8, 5.1), 2.78 (1 H, td, *J* 0.5, 4.6), 2.94 (1 H, dtt, *J* 5.2, 2.6, 3.9) and 5.11 (1 H, tsept, *J* 1.2, 6.8). δ_C (100 MHz, $CDCl_3$) 17.6, 19.5, 25.4, 25.7, 30.6, 37.3, 39.8, 47.5, 51.1, 124.5 and 131.3. ν_{max} (Si pellet, liquid film, cm^{-1}) 702, 822, 1114, 1428, 2857 and 2930. HRMS (EI, 40 °C, 70 eV) found 168.1509. $C_{11}H_{20}O$ requires 168.1514. m/z (EI, 40 °C) 168 (M^+, 0.8%), 150 (13), 135 (36), 123 (11), 109 (35), 95 (91), 81 (77), 69 (100) and 55 (78). $[\alpha]_D^{20}$+33.8 (0.94, $CHCl_3$).
(2*S*,4*S*)-4,8-dimethylnon-7-en-1,2-diol (**7**):
δ_H (400 MHz, $CDCl_3$) 0.94 (3 H, d, *J* 6.6), 1.09-1.19 (1 H, m), 1.37-1.45 (3 H, m), 1.58 (1 H, m), 1.60 (3 H, s), 1.68 (3 H, s), 1.89-2.08 (2 H, m), 2.45-2.70 (2 H, bm), 3.39 (1 H, dd, *J* 8.1, 10.6), 3.64 (1 H, bd, *J* 10.9), 3.80 (1 H, bq, *J* 6.6) and 5.09 (1 H, tsept, *J* 7.1, 1.4). δ_C (100 MHz, $CDCl_3$) 17.6, 20.2, 25.3, 25.7, 29.2, 36.7, 40.5, 66.9, 70.5, 124.6 and 131.3. ν_{max} (Si pellet, liquid film, cm^{-1}) 1066, 1377, 1458, 2924 and 3367 b. HRMS (EI, 60 °C, 70 eV) found 186.162. $C_{11}H_{22}O_2$ requires 186.1620. m/z (EI, 60 °C) 186 (M^+, 11%), 169 (7), 155 (13), 137 (17), 123 (7), 109 (32), 95 (44), 86 (94), 84 (100) and 69 (82). $[\alpha]_D^{20}$ -10.3 (1.38, $CHCl_3$).

Conversion of 7 into 8:
TBDPSCl (0.20 mL, 0.77 mmol) and imidazole (56 mg, 0.92 mmol) were added to a solution of diol **7** (143 mg, 0.77 mmol) in DMF (1.5 mL) and the resulting solution allowed to stir overnight. The reaction was quenched by addition of water and ethyl acetate and the layers partitioned. The aqueous phase was extracted three times with ethyl acetate and the combined organic extracts washed twice with water, once with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with hexane −ethyl acetate (10:1), to yield (2*S*,4*S*)-1-{[*tert*-butyl(diphenyl)silyl]oxy}-4,8-dimethylnon-7-en-2-ol (308 mg, 94%) as a clear, colorless oil.
δ_H (400 MHz, $CDCl_3$) 1.09 (9 H, s), 1.10 (1 H, m), 1.29-1.42 (3 H, m), 1.55 (1 H, m), 1.59 (3 H, s), 1.68 (3 H, s), 1.93 (1 H, m), 2.00 (1 H, m), 2.51 (1 H, d, *J* 3.3), 3.47 (1 H, dd, *J* 4.7 10.0), 3.66 (1 H, dd, *J* 3.2, 10.2), 3.82 (1 H, m), 5.09 (1 H, tt, *J* 1.3, 7.1), 7.43 (6 H, m) and 7.69 (4 H, m). δ_C (100 MHz, $CDCl_3$) 14.2, 17.6, 19.2, 20.1, 25.3, 25.7, 26.9, 29.3, 36.8, 40.1, 68.2, 70.2, 124.8, 127.7, 127.8, 129.8 (2 signals), 131.1, 133.2 (2 signals) and 135.5 (2 signals). ν_{max} (Si pellet, liquid film, cm^{-1}) 702, 1113, 1261, 1428, 1462, 1472, 2858, 2929, 3071 and 3583 b. HRMS (EI, 90 °C, 70 eV) found 367.2101. $C_{23}H_{31}O_2Si$ requires 367.2093. m/z (EI, 90 °C) 367 (M^+ - Bu, 17%), 241 (42), 199 (100), 181 (41), 123 (71) and 77 (70). $[\alpha]_D^{20}$ −0.82° (1.82, $CHCl_3$).
TEA (0.14 mL, 1.00 mmol) and MsCl (54 μL, 0.68 mmol) were added to a solution of (2*S*,4*S*)-1-{[*tert*-butyl(diphenyl)-silyl]oxy}-4,8-dimethylnon-7-en-2-ol (258 mg, 0.61 mmol) in DCM (4 mL) at 0 °C and the solution stirred for 15 min. After this time, the reaction was quenched by addition of an ammonium chloride solution and the layers partitioned. The aqueous phase was extracted three times with DCM, the combined organic extracts washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was redissolved in THF (4 mL) and TBAF (0.7 mL, 1.0 M in THF, 0.7 mmol) was added. The solution was stirred for 10 min, then a 20% aqueous solution of NaOH (7 mL) was added and the mixture stirred for 20 min. After this time, the mixture was diluted with ether and the layers partitioned. The organic phase was washed with water then brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with hexane − toluene (1:20), to yield **8** (91 mg, 89%) as a clear, colorless oil.
(2-{(2*R*,6*R*)-6-[(2*S*)-4-(Bromomethyl)-2-methylpent-4-enyl]-5,6-dihydro-2*H*-pyran-2-yl}ethoxy)(*tert*-butyl)-dimethylsilane (3)
Triphenylphosphine (640 mg, 2.40 mmol) and carbon tetrabromide (800 mg, 2.40 mmol) were added to a solution of 2-{(2*S*)-3-[(2*R*,6*R*)-6-(2-[(*tert*)-butyl{dimethyl}silyloxy]-ethyl)-3,6-dihydro-2*H*-pyran-2-yl]-2-methylpropyl}prop-2-en-1-ol (650 mg, 1.80 mmol) in acetonitrile (20 mL) at 22 °C and the solution stirred for 10 min. After this time, the reaction was quenched by addition of $NaHCO_3$ solution and diluted with ether. The layers were partitioned and the aqueous phase was extracted three times with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography, eluting with hexane − ethyl acetate (20:1), to yield the title compound and excess triphenylphosphine as a mixture that could only be separated by HPLC. 490 mg (65%) of **3** was obtained as a clear, colorless oil.
δ_H (250 MHz, $CDCl_3$) 0.08 (6 H, s), 0.91 (9 H, s), 0.92 (3 H, m), 1.19 (1 H, ddd, *J* 3.3, 9.9, 13.6), 1.54-1.75 (2 H, m), 1.78-2.25 (6 H, m), 3.65-3.84 (3 H, m), 3.95 (1 H, d, *J* 10.1), 4.00

(1 H, d, *J* 10.1), 4.34 (1 H, m), 4.98 (1 H, d, *J* 0.7), 5.22 (1 H, s), 5.70 (1 H., m) and 5.81 (1 H, ddt, *J* 5.4, 9.9, 1.9). δ_C (62.5 MHz, $CDCl_3$) -5.3, 18.3, 19.3, 26.0, 26.6, 31.5, 36.6, 36.8, 41.7, 42.5, 59.9, 64.7, 69.5, 116.6, 124.0, 130.0 and 144.0. ν_{max} (Si pellet, liquid film, cm^{-1}) 836, 1095, 1256, 1391, 1437, 1462, 2857 and 2928. m/z (EI, 40 °C) 359 (M+- Bu, 0.3%), 337 (2), 205 (7), 187 (46), 155 (27), 125 (59), 107 (56), 81 (100). $[\alpha]_D^{20}$ −36.1 (1.38, $CHCl_3$).

Article Identifier:
1437-2096,E;2001,0,07,1105,1108,ftx,en;G06401ST.pdf