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Synthesis of Novel 11-Desmethyl Analogues of Laulimalide by Nozaki–Kishi Coupling

Ian Paterson,*,† Hermann Bergmann,† Dirk Menche,† and Albrecht Berkessel‡

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K., and Institut für Organische Chemie der Universität zu Köln, Greinstrasse 4, D-50939 Köln, Germany

ip100@cam.ac.uk

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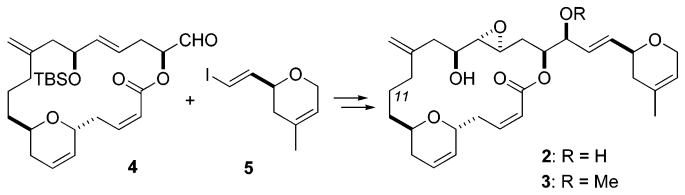
ABSTRACT



As a first entry into structurally simplified analogues of the anticancer agent laulimalide, 11-desmethyl compounds 2 and 3 were selected by molecular modeling. The unfavorable diastereoselectivity in the key synthetic step, a Nozaki–Kishi coupling between macrocyclic aldehyde 4 and vinyl iodide 5, was overcome either by use of catalytic amounts of DIANANE-type ligands or L-Selectride reduction of the derived enone. This methodology should allow modular introduction of other, unnatural, side chains.

By sharing the same microtubule-stabilizing mechanism as Taxol and having nanomolar growth inhibitory activity against cancer cell lines, including multidrug resistant cells, laulimalide (**1**, Scheme 1) presents a promising lead structure for development of new anticancer agents.[1,2] However, in comparison to Taxol and other known microtubule-stabilizing agents, laulimalide appears to have a different (and as yet undefined) binding site on tubulin.[3]

This unique biological profile, together with the low natural abundance from its sponge sources, has triggered numerous synthetic efforts which have culminated in a multitude of total syntheses, including one from our group.[4−6]

In contrast, a limited range of analogues, relying primarily on modifying the hydroxyls, the (*Z*)-enoate, or removal of the epoxide, have been reported to date for SAR studies.[1a,3,6] Herein, we report the total synthesis of 11-*desmethyl*-laulimalide (**2**) and its methyl ether **3** by a novel approach, relying on an asymmetric Nozaki−Kishi coupling of the macrocyclic aldehyde **4** with dihydropyran containing vinyl

† University of Cambridge.
‡ Universität zu Köln.

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(3) Pryor, D. E.; O'Brate, A.; Bilcer, G.; Diaz, J. F.; Wang, Yu.; Wang, Yo.; Kabaki, M.; Jung, M. K.; Andreu, J. M.; Ghosh, A. K.; Gianna-kakou, P.; Hamel, E. *Biochemistry* **2002**, *41*, 9109.

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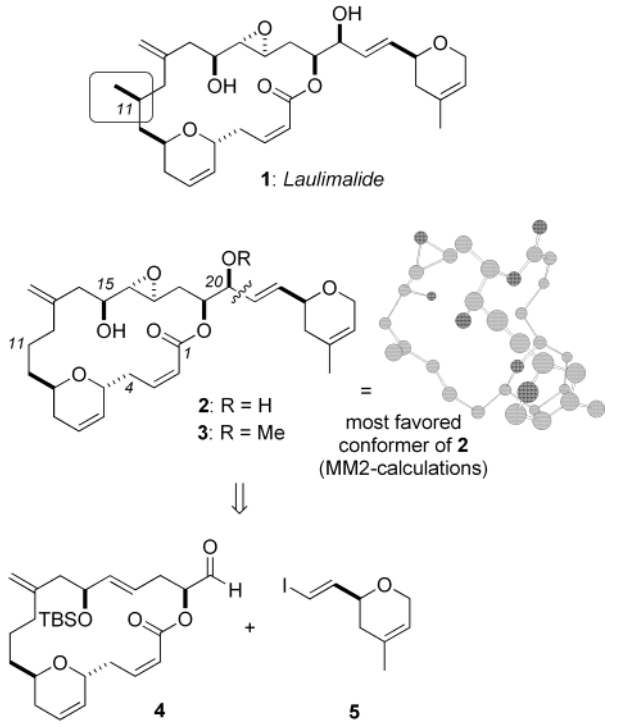
Scheme 1



iodide **5**. Notably, this synthesis design should enable the modular construction of a wide range of laulimalide analogues with unnatural side chains.

Based on molecular modeling, 11-desmethyl analogues of laulimalide were chosen as a first, promising series of simplified structures.[7] In particular, these were expected to adopt conformations closely related to **1** in the presumably crucial C_1-C_4 and $C_{15}-C_{20}$ regions.[1a,6]

To allow for a high degree of convergence, our synthesis of the macrocyclic ring **4** (Scheme 2) was based on previously established[5c] diastereoselective aldol coupling using chiral boron enolate methodology of the C_1-C_{14} subunit **7** with $C_{15}-C_{19}$ subunit **6**, followed by a Mitsunobu-type macrolactonization. Conjugate reduction of enone **8** using Stryker's reagent[8] and Takai methylenation[9] of the ketone group proceeded smoothly (77%) and allowed the preparation of building block **9** in a reliable and scalable process. This was transformed into aldehyde **4** by selective deprotection to reveal the primary hydroxyl (TBAF/AcOH) followed by Swern oxidation (60%).

(7) The 3-dimensional structures of **1** and **2** were obtained by 10 000-step Monte Carlo conformational searches with MacroModel 8.0 using the MM2*-force field and the generalized Born/surface area (CB/SA) solvent model and the crystal structure data of **1**[2c] as input geometries: (a) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Kiskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127. A series of closely related conformers of **1** and **2** were found within 3.00 kcal/mol of the global minima both in water and chloroform.

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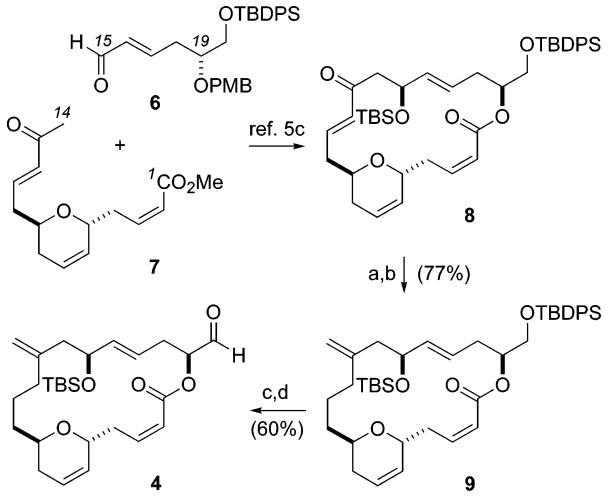
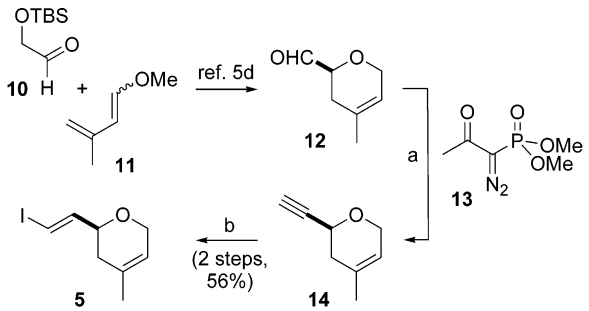
Scheme 2[a]



[a] Conditions: (a) $[CuHPPh_3]_6$, benzene (wet), rt; (b) Zn, TMSCl, CH_2I_2, $TiCl_4$, PbI_2, THF; (c) TBAF/AcOH (pH 7), THF, 0 °C to rt, 72 h, 82%; (d) $(COCl)_2$ (15 equiv), DMSO (30 equiv), NEt_3 (70 equiv), CH_2Cl_2, −78 to −10 °C.

Following our earlier route,[5d] the dihydropyran unit of the authentic side chain of laulimalide was conveniently prepared by application of the Jacobsen HDA reaction[10] of aldehyde **10** and diene **11** (Scheme 3).[5d] After homologation of

Scheme 3[a]



[a] Conditions: (a) K_2CO_3, MeOH; (b) Cp_2ZrHCl, CH_2Cl_2; I_2.

aldehyde **12** with the Ohira−Bestmann reagent **13**,[11] hydrozirconation of the derived alkyne **14**, and trapping of the organometallic species with iodine,[12] the vinyl iodide **5** was obtained.

For the pivotal coupling of **5** with aldehyde **4**, we chose an asymmetric variant of the Nozaki−Kishi reaction,[13]

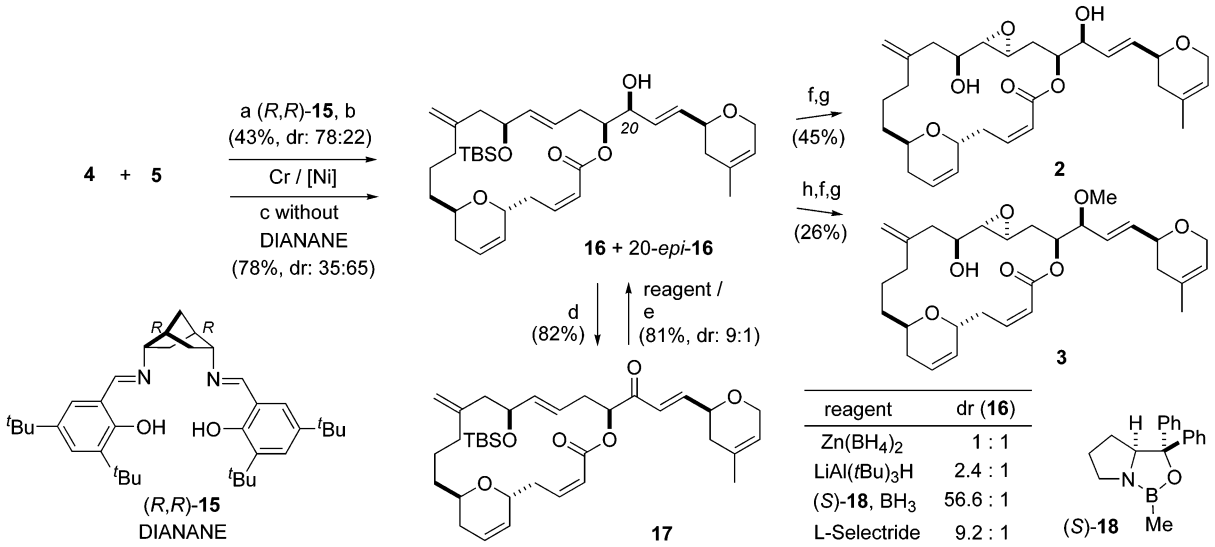
(10) Jacobsen, E. N.; Dossetter, A. G.; Jamison, T. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398.

(11) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

(12) Schwartz, J.; Carr, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 2927.

(13) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. (b) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (c) Choi, H.-W.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435.

Scheme 4[a]



[a] Conditions: (a) (*R*,*R*)-**15** (10 mol %), $CrCl_2$ (10 mol %), $NiCl_2$ (2 mol %), NEt_3 (20 mol %), Mn, TMSCl, THF; (b) TBAF/AcOH (pH 7), THF, 0 °C to rt; (c) $CrCl_2$, $NiCl_2$, THF/DMF; (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 to −10 °C; (e) L-Selectride, THF, −78 °C; (f) HF/pyridine, THF; 0 °C to rt; (g) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, 4 Å MS, CH_2Cl_2, −20 °C; (h) $Me_3O^+BF_4^-$, Proton Sponge, CH_2Cl_2.

developed by our groups using C_2-symmetric DIANANE-type salen ligands (Scheme 4).[14] Employing catalytic amounts of the chromium(II) complex of (*R*,*R*)-**15**, preformed in situ using our previously reported protocol,[14a] overcame the substrate selectivity in this coupling and gave allylic alcohol **16** with the desired configuration and useful levels of stereoinduction (dr 78:22). In contrast, the matched reaction, using (*S*,*S*)-**15**, almost exclusively gave the undesired 20-*epi*-**16** (dr 94:6, not shown). Notably, these addition reactions represent one of the first examples of synthetically useful levels of asymmetric induction being realized for catalytic, enantioselective Nozaki−Kishi couplings in complex coupling partners.[13c] With the recently developed[14b] efficient large-scale enantioselective synthesis of the diamine backbone of **15** it is very promising to now develop and also evaluate structural analogues of these novel salen-type ligands. For preparative purposes, it proved convenient to enhance the diastereomeric ratio in favor of **16** by a two-step oxidation−reduction sequence via enone **17**. Among the reagents screened, L-Selectride gave optimal results with respect to both chemo- and stereoselectivity.[15,16] Subsequent TBS deprotection followed by a highly selective Sharpless epoxidation[5d,e] completed the synthesis of 11-*desmethyl*-laulimalide (**2**). Its methyl ether **3**[17] was prepared by utilizing the same sequence after methylation of the C_{20}-hydroxyl in **16**. This derivative was selected to mitigate the inherent intramolecular nucleophilicity of the C_{20}-hydroxyl group toward the epoxide (leading to isolaulimalide), which will be crucial to transform laulimalide into a true drug candidate.[18]

In summary, based on conformational analysis, we have prepared 11-desmethyl analogues of laulimalide representing a structural simplification of this antimitotic macrolide. Our convergent approach relies on separate construction of the macrocyclic core and the side chain and assembly of these two units by a Nozaki−Kishi reaction. For this coupling, use of DIANANE-based salen ligands succeeded in overcoming the undesired substrate facial bias in a mismatched situation. This approach established herein should enable the introduction of a variety of different side chains.

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Supporting Information Available: Full characterization of all new compounds and copies of NMR spectra for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Use of oxazaborolidine mediated borane reduction with (*S*)-**18** gave better diastereoselectivity but proceeded with only moderate yields.

(16) The configuration of **16** was deduced from model studies and is in agreement with the expected selectivity of the Nozaki−Kishi reaction[14a] and was further confirmed by the close similarity of the NMR data for **2** and **1** and their precursors.[5d]

(17) During the course of our studies, the Wender group disclosed the synthesis and biological evaluation of the corresponding methyl ether of laulimalide; see ref 6b.

(18) First, biological evaluation suggests **2** to be of very similar potency to laulimalide, while **3** is less active. Full details will be reported elsewhere.