signals of the keto form are given): $\delta = 4.31$ (m, 1H; C*H*OH), 3.62 (dd, $J = 11.2$, 5.1 Hz, 1H; H-6), 3.57 (dd, $J = 11.2$, 5.0 Hz, 1H; H-6), 3.41 (s, 2H; H-2), 3.10 (br s, 1H; OH), 2.90 (dd, $J = 17.5$, 5.0 Hz, 1H; H-4), 2.83 (dd, $J = 17.5$, 7.3 Hz, 1H; H-4), 1.47 (s, 9H, $C(CH_3)_3$); $^{13}C$ NMR (75.5 MHz, $CDCl_3$, 20 °C, only signals of the keto form are given): $\delta =$ 28.1 ($C(CH_3)_3$), 46.6, 48.4, 51.3 (C-2, C-4, C-6), 67.6 (C-5), 82.7 ($C(CH_3)_3$), 166.2 (C-1), 202.9 (C-3).

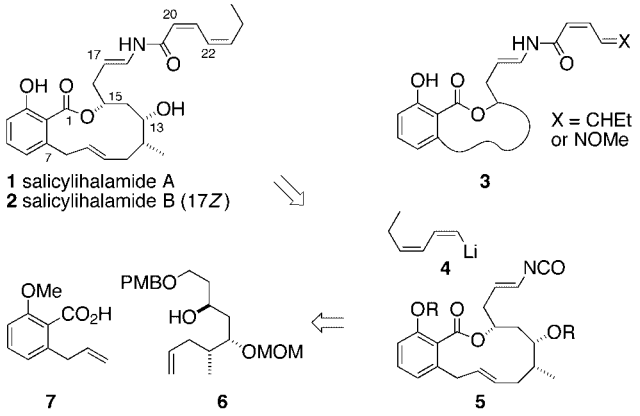
[15] The diastereomeric excess was determined by GC after formation of the corresponding acetonides (2,2-dimethoxypropane, cat. camphorsulfonic acid).

## Revision of the Absolute Configuration of Salicylihalamide A through Asymmetric Total Synthesis**

Yusheng Wu, Lothar Esser, and Jef K. De Brabander*

Natural products that elicit a specific and unique biological response in mammalian cells represent valuable tools to identify, study, and target possible new gene products. In this context, the recent isolation of salicylihalamides A and B (**1** and **2**, Scheme 1) from the marine sponge *Haliclona* sp. is noteworthy.[1] Pattern-recognition analysis of their unique differential 60-cell mean-graph screening profiles (National Cancer Institute) suggests that the salicylihalamides belong to a potentially new mechanistic class of antitumor compounds.[1] Since their discovery in 1997, an emerging class of novel bioactive metabolites have been isolated that structurally relate to the salicylihalamides by virtue of an unprecedented highly unsaturated enamide attached to a macrocyclic salicylate (generalized structure **3**, Scheme 1). These include the mechanistically related lobatamides,[2] the potent cytostatic apicularens,[3] and selective inhibitors of oncogene-transformed cells (oximidines),[4] as well as compounds that induce low density lipoprotein (LDL) receptor gene expression.[5] The opportunity to develop chemistry in this area—none of these compounds have been synthesized previously—as well as to access variants for mode of action studies, prompted us to initiate a synthetic program towards this intriguing class of natural products.[6] Herein, we disclose the total synthesis of **1** and demonstrate unequivocally that the absolute configuration of natural (−)-salicylihalamide A, formulated as **1** through Mosher's ester $^1H$ NMR spectroscopic experiments by the group who isolated it,[1] was misassigned.

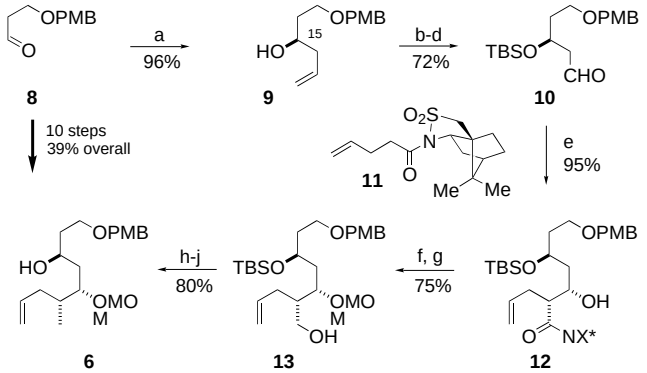
From the onset, we deemed it crucial to introduce the sensitive *N*-(alkenyl)heptadienamide side chain at a late stage in the synthesis (Scheme 1). Considering the options, we felt




Scheme 1. Synthetic strategy for salicylihalamide A. PMB = *para*-methoxybenzyl, MOM = methoxymethyl.

that the addition of 1-lithio-1,3-hexadiene (**4**) to isocyanate **5** would offer the distinct advantage of mild reaction conditions and control of stereochemistry.[7] Isocyanate **5** was to be derived from the corresponding *E*-$\alpha,\beta$-unsaturated carboxylic acid (acyl azide formation/Curtius rearrangement), in turn accessible from a C17 aldehyde by Horner–Wadsworth–Emmons homologation. A Mitsunobu esterification/olefin ring-closing metathesis (RCM) tactic would ultimately unravel the 12-membered benzolactone ring into its primary components, polyol fragment **6** and benzoic acid derivative **7**.

A fully optimized procedure, delivering gram quantities of alcohol **6**, is presented in Scheme 2. We opted for an




Scheme 2. Reagents and conditions: a) 2-$^d$Icr$_2$B(allyl),[8] $Et_2O$, −78 °C, then NaOOH, 96%; b) TBSCl, imidazole, DMAP, DMF, 94%; c) cat. $OsO_4$, NMO, acetone/$H_2O$; d) $Pb(OAc)_4$, pyridine, PhH, 77% (steps c, d); e) **11**, $TiCl_4$, *i*$Pr_2$NEt, $CH_2Cl_2$, −78 °C, then **10**, −78 °C, 95%; f) MOMCl, NaI, *i*$Pr_2$NEt, $CH_2Cl_2$, 91%; g) $LiEt_3BH$, THF, −78 °C → RT, 82%; h) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 91% (5% recovery of **13**); i) $LiEt_3BH$, THF, −78 °C → RT, 90%; j) TBAF, THF, 98%. Icr = isocaranyl, TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, DMF = dimethylformamide, NMO = 4-methylmorpholine *N*-oxide, RT = room temperature, Ts = tosyl = toluene-4-sulfonyl, TBAF = tetrabutylammonium fluoride, X* = boranesultam.

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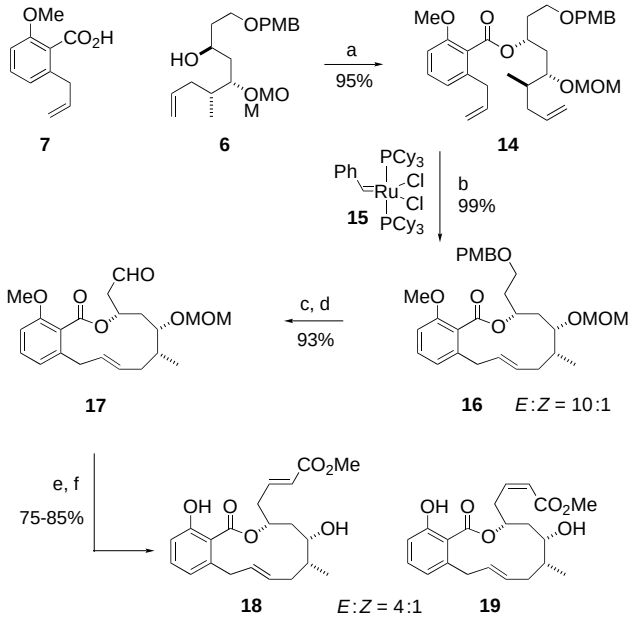
enantioselective allylation of aldehyde **8** to set the absolute stereochemistry at C15.[8] The corresponding homoallyl alcohol **9**, obtained in 96% yield, was silylated followed by oxidative double-bond cleavage (72% yield, 3 steps). Treatment of the corresponding aldehyde **10** with the in situ prepared *Z*-(*O*)-titanium enolate[9] derived from (2*R*)-*N*-(4-pentenoyl)bornanesultam (**11**)[10] produced exclusively one diastereomeric aldol product **12** in 95% yield.[11] Reduction of the corresponding MOM ether delivered primary alcohol **13** (75%, 2 steps), which was further converted into **6** by tosylate formation, reduction, and fluoride-assisted liberation of the C15 alcohol (80%, 3 steps).

Setting the stage for the RCM,[12] fragment **6** was joined with carboxylic acid **7**[13] through a Mitsunobu inversion (Scheme 3).[14] Exposure of **14** to a catalytic amount of Grubbs' ruthenium carbene complex **15**[15] preferentially

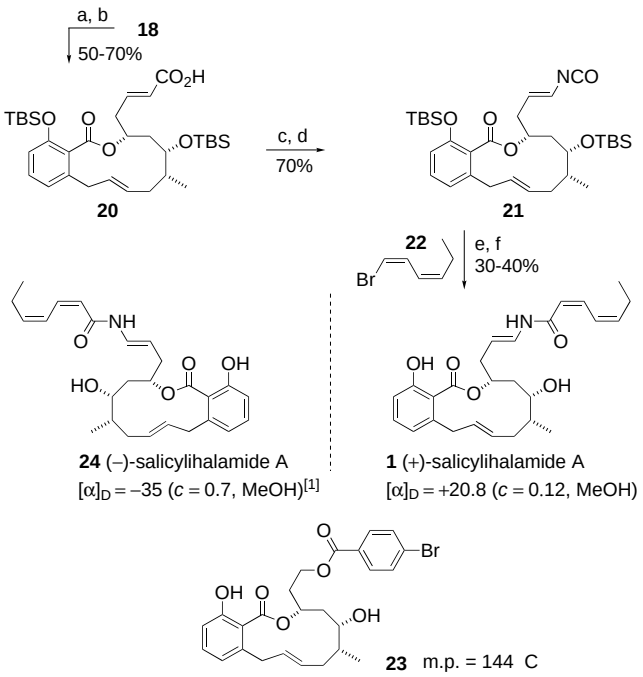



Scheme 3. Reagents and conditions: a) DEAD, $PPh_3$, $Et_2O$, 95%; b) 10 mol% $[(Cy_3P)_2Cl_2Ru{=}CHPh]$ (**15**), $CH_2Cl_2$, 99%; c) DDQ, $CH_2Cl_2$/$H_2O$, 96%; d) Dess–Martin periodinane, $CH_2Cl_2$, 97%; e) trimethyl phosphonoacetate, NaH, THF, 0 °C, 90%; f) $BBr_3$, $CH_2Cl_2$, −78 °C, 90% (**18**:**19** = 4:1). DEAD = diethylazodicarboxylate, Cy = cyclohexyl, DDQ = 2,3-dichloro-4,6-dicyano-1,4-benzoquinone.

produced the desired *E* isomer **16** with an impressive (and reproducible!) selectivity of 10–11:1 (*E*:*Z*).[16] Moving forward, **16** was oxidatively deprotected (DDQ) and further oxidized to aldehyde **17** by exposure to Dess–Martin periodinane (93%, 2 steps).[17] At this stage, we had achieved an extremely efficient synthesis of the lactone core of the salicylihalamides, delivering gram quantities of **17** in 34% overall yield from aldehyde **8** (14 steps).

All that remained to complete the total synthesis was the introduction of the side chain followed by final deprotection. Thus, following homologation of aldehyde **17** with trimethyl phosphonoacetate (NaH, THF), treatment with $BBr_3$ led to the corresponding *E*- and *Z*-methyl esters **18** and **19** (4:1), which were separated by flash column chromatography (silica, EtOAc/hexanes (35/65)).[18]

Hydrolysis ($Ba(OH)_2 \cdot 8H_2O$) of the major *E*-methyl ester **18** was followed by complete silylation with excess TBSCl (Scheme 4). Upon workup, silylester hydrolysis had occurred,




Scheme 4. Reagents and conditions: a) $Ba(OH)_2 \cdot 8H_2O$, MeOH; b) TBSCl, imidazole, DMF, 50–70% (from **18**); c) $(PhO)_2P(O)N_3$, $Et_3N$, PhH; d) PhH, 80 °C, 70% (from **20**); e) **22**, *t*BuLi, $Et_2O$, −78 °C, then add **21**, −78 °C → 0 °C, 55–65%; f) HF · pyridine, pyridine/THF, 40–60%.

allowing the corresponding acid **20** to be converted into isocyanate **21** as shown. We were now in a position to explore the crucial installation of the dienamide side chain. Incorporation proceeded smoothly through the addition of hexadienyllithium, prepared in situ from bromide **22**[19] by metal–halogen exchange (*t*BuLi), to a −78 °C solution of isocyanate **21** (pure compound according to chromatographic analysis).[7b] The total synthesis was completed by deprotection of the silylether protecting groups with HF · pyridine (1:1) in THF, to afford synthetic salicylihalamide A (**1**).[20] This material was found to be identical to natural salicylihalamide A according to NMR ([$D_6$]benzene and [$D_4$]methanol), IR, and UV spectroscopy, as well as HPLC, and thin layer chromatography (3 different solvent systems).[21]

We were completely surprised, however, that the optical rotation of synthetic salicylihalamide A (**1**) was of opposite sign ($[\alpha]_D^{23} = +20.8$ ($c = 0.12$, MeOH)) to the optical rotation recorded for natural salicylihalamide A ($[\alpha]_D^{23} = -35$ ($c = 0.7$, MeOH)).[1] Moreover, synthetic **1** was completely ineffective (up to 20 μM) in arresting the growth of SK-MEL-28, a human melanoma cancer cell-line reported to be sensitive to natural salicylihalamides with a $GI_{50}$ of 100 nM ($GI_{50}$ = the concentration at which growth of 50% of the cells is inhibited).[1] At this point we had the fortune that *para*-bromobenzoate derivative **23**[22] provided crystals suitable for X-ray diffraction studies, confirming the absolute configuration of our synthetic lactones.[23] Based on all the available evidence, the absolute configuration of natural (−)-salicyli-

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halamide A was revised unambiguously to the one represented by structure **24** (*ent*-**1**).

In summary, we have accomplished the first synthesis of (+)-salicylihalamide A and revised the absolute configuration of the natural product to 12*S*,13*R*,15*S*. Our approach features a highly efficient, *trans*-selective ring-closing olefin metathesis for the assembly of the 12-membered salicylate skeleton and can be readily adapted to obtain the natural enantiomer.

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[18] Note that **19** is a useful intermediate for the synthesis of *ent*-salicylihalamide B (**2**).

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[20] The 22*E* isomer (≈20%) was removed by preparative HPLC (normal phase, acetone/hexanes (3/7)).[19]

[21] A sample and the NMR spectra of natural (−)-salicylihalamide A were kindly provided by Dr. M. R. Boyd, National Cancer Institute (Frederick, MD, USA).

[22] This derivative was prepared from **16**: 1) DDQ, CH$_2$Cl$_2$/H$_2$O, RT; 2) *para*-bromobenzoic acid, PPh$_3$, DEAD, Et$_2$O, RT; 3) BBr$_3$ (3 equiv), CH$_2$Cl$_2$, −78 °C.

[23] Crystallographic data (excluding structure factors) for the structure reported in this paper (**23**) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-147019. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).


## Clean and Efficient Catalytic Reduction of Perchlorate**

Mahdi M. Abu-Omar,* Lee D. McPherson, Joachin Arias, and Virginie M. Béreau

Even though perchlorate is a strong oxidizing agent thermodynamically [Eq. (1)], its reactions are very slow

$$ClO_4^- + 2H^+ + 2e^- \longrightarrow ClO_3^- + H_2O \quad (1)$$
$$E^o = 1.23\ V$$

because it is nonlabile.[1–3] Consequently, perchlorate salts are often used to adjust ionic strength in kinetics and electrochemical investigations. Perchlorate is also a poor complexing ("innocent") anion.[4] In 1997, $ClO_4^-$ was found in ground and surface waters in several U.S. western states at concentrations up to 3700 mg L$^{-1}$.[5–7] For example, 30% of the wells sampled


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