Total synthesis of aspercyclide C†

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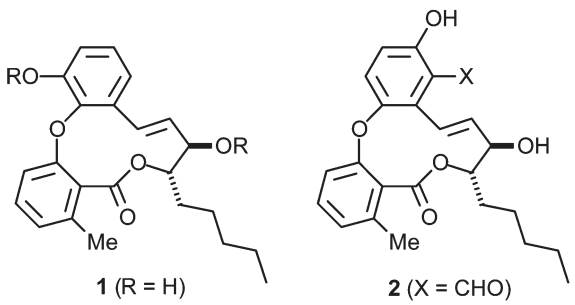
The first total synthesis of (+)-aspercyclide C (1) is reported using a kinetically controlled RCM reaction to form the 11-membered, unsaturated lactone ring of this bioactive diaryl ether macrolide.

Binding of immunoglobulin E (IgE) to the human high-affinity IgE receptor FcεRI located in the membrane of mast cells and basofils is a pivotal step in triggering allergic disorders.[1] Upon cross linking of the resulting IgE·FcεRI complex by multivalent allergens, a signal transduction cascade is activated which can ultimately manifest itself in diseases such as allergic rhinitis or asthma. Although IgE and its high affinity receptor therefore constitute highly relevant biochemical targets, any "anti-IgE therapy" copes with the problem of how to selectively disrupt the interaction between two large proteins.[2] Hence, it may not come as a surprise that small molecule IgE-antagonists are essentially unknown.[3]

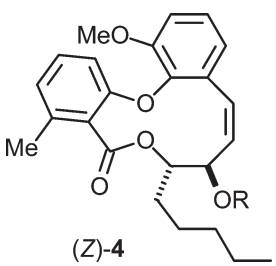


1 (R = H)
(*E*)-**4** (R ≠ H)

2 (X = CHO)
3 (X = CH_2OH)

Only recently, a group at Merck has reported the isolation of a family of natural products claimed to exert such a function. Though only moderately active (IC_{50} of 200 μM for aspercyclide A (**2**)), the aspercyclides **1–3** constitute a very first hit meriting further investigation.[4] These fungal metabolites were extracted from the culture broth of an *Aspergillus* sp. derived from a soil sample collected in Tanzania. They consist of an 11-membered unsaturated lactone moiety flanked by a differently substituted diaryl ether backbone. While these structural features invite a host of modifications that should allow for a detailed mapping and optimisation of structure/activity relationships, the rather strained nature of the targets sets serious limitations as to the methods that can be applied. Outlined below is the first total synthesis of aspercyclide C **1** aiming to explore some of these possibilities.

Encouraged by previous successful implementations of ring closing metathesis (RCM) into the total synthesis of natural products containing medium sized rings,[5] we chose this methodology for the formation of the lactone moiety in **1**. Despite the now well established fact that RCM can provide access to virtually all ring sizes ⩾5,[6] applications to 11-membered carbo- and heterocycles remain scarce and are sometimes rather low yielding.[7] Moreover, one has to keep in mind that RCM usually affords (*E*,*Z*)-mixtures whenever the incipient ring is large enough to accommodate both isomers, as is the case in aspercyclide C. The only method to impose selectivity on the formation of a medium sized ring by RCM known to date relies upon 'thermodynamic *vs.* kinetic control' during ring closure. This strategy was developed as part of a recent total synthesis of the herbicidal decalactone herbarumin and allowed for the first deliberate preparation of either stereoisomer of a given olefinic target.[8] Specifically, advantage was taken of the fact that 'second generation' catalysts will scramble the newly formed olefin and hence deliver the thermodynamic cycloalkene,[9] whereas the use of less active 'first generation' catalysts allows trapping of the kinetic isomer. Provided that the (*E*)- and (*Z*)-isomer of a medium sized cycloalkene are sufficiently different in energy, good levels of stereoselectivity can be attained.[8]



(*Z*)-**4**

Unfortunately, however, this useful concept seems to find its limitations in the projected case. According to our semi-empirical calculations, the *O*-protected stereoisomer (*E*)-**4** is only ⩽ 1.8 kcal mol^{-1} more stable than its isomer (*Z*)-**4**,‡ thus making appreciable levels of thermodynamic control during RCM rather unlikely. Because possible kinetic preferences during ring closure remain difficult to predict,[10] the aspercyclide C case highlights once more the as yet incomplete understanding of and missing reagent-control over metathetic transformations.[11]

Despite these concerns, a total synthesis of **1** was pursued starting from commercial 2-methyl-6-nitrobenzoic acid (Scheme 1). Esterification followed by reduction of the nitro group in **5** with H_2 over Pd/C and conversion of the resulting aniline **6** to the corresponding aryl bromide by a Sandmeyer reaction gave

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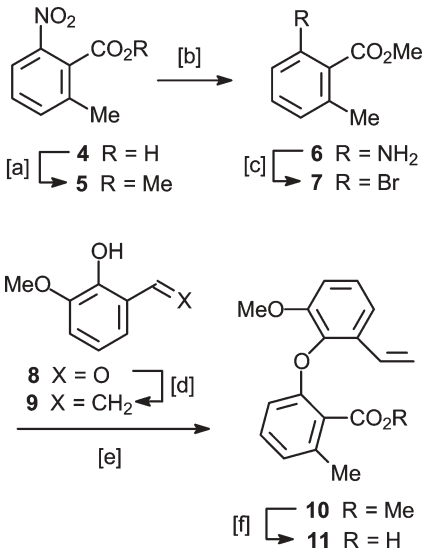
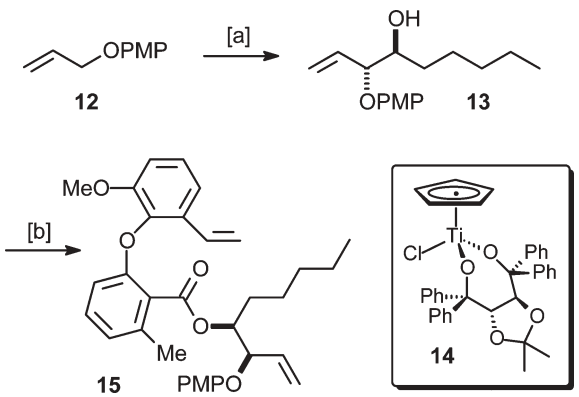
† Electronic supplementary information (ESI) available: Experimental procedure for the oxyallylation and the RCM reaction, spectroscopic data of compounds **13** and **17**, and copies of pertinent NMR spectra. See DOI: 10.1039/b512877c



Scheme 1 *Reagents and conditions*: [a] MeI, K_2CO_3, acetone, reflux, 98%; [b] H_2 (1 atm), Pd/C (10% *w/w*), EtOH, quant.; [c] $NaNO_2$/HBr; then CuBr, HBr, 0 °C → r.t., 97%; [d] Ph_3PCH_3Br, NaHMDS (2.1 equiv.), THF, 70%; [e] CuO, K_2CO_3, pyridine, 130 °C, 55%; [f] aq. NaOH, MeOH, then aq. HCl quant.

multigram amounts of **7**. Ullmann coupling[12] of this compound with phenol **9** (accessible in 70% yield in one step from commercial aldehyde **8**, PPh_3CH_3Br and 2.1 equiv. of NaHMDS) was promoted by CuO and K_2CO_3 in pyridine at 130 °C (sealed tube),[13] affording product **10** in 55% isolated yield. This outcome is respectable in view of the crowded neighbourhood of the diaryl ether bridge. Saponification of the methyl ester under standard conditions gave acid **11** without incident.

An *anti*-selective Duthaler–Hafner oxy-allylation reaction[14–16] provided rapid access to the aliphatic segment in optically active form (Scheme 2). Specifically, deprotonation of allyl *p*-methoxyphenyl (PMP) ether **12** with *sec*-BuLi at −78 °C followed by transmetallation of the resulting allyllithium species with (*S*,*S*)-**14** furnished an organotitanium reagent which transferred its functionalized allyl substituent to hexanal to give homoallyl alcohol **13** in 69% isolated yield (*anti* : *syn* > 95 : 5, ee = 92%). Although the esterification of this compound with acid **11** turned

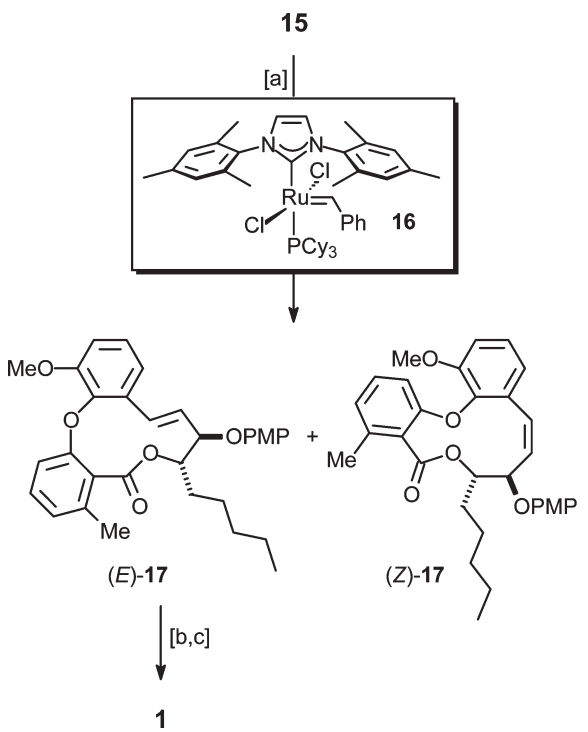


Scheme 2 *Reagents and conditions*: [a] *sec*-BuLi, then complex **14**, hexanal, THF/Et_2O, −78 °C, 69%; [b] acid **11**, *N*-methyl-2-chloropyridinium iodide, Et_3N, MeCN, reflux, 82%.

out to be more difficult than anticipated, good yields of diene **15** could be secured by the Mukaiyama method,[17] thus setting the stage for the envisaged closure of the medium sized ring by RCM.

As outlined above, our semi-empirical calculations had shown that both stereoisomers of the resulting cycloalkene are similar in energy, thus suggesting that thermodynamic control should be counterproductive in this particular case. As a result, an attempt was made to cyclize diene **15** with the aid of the 'first generation' Grubbs carbene complex $(PCy_3)_2Cl_2Ru$=CHPh which is known to equilibrate cycloalkenes only slowly due to its reduced activity towards disubstituted olefins.[18] Although ring closure remained incomplete (⩽ 50% conversion after 5 d at 80 °C using up to 50 mol% of catalyst added in portions over the course of the reaction), NMR inspection of the crude product showed that (*E*)-**17** had formed exclusively, indicating that the desired isomer must be kinetically favoured. Gratifyingly, the 'second generation' complex **16** (20 mol%, added in 2 portions) bearing an *N*-heterocyclic carbene ligand[19] also gave appreciable selectivity, even though scrambling of the product initially formed should be more facile due to the higher reactivity of this catalyst. The reaction was best performed in dilute (2 mM), *refluxing* toluene solution,[20] giving product **17** in 69% yield with an *E* : *Z* ratio of 5 : 1 after 4 h reaction time (Scheme 3). The fact that the isomer distribution did not change significantly with time even though fresh catalyst was introduced in portions over the course of the reaction can only be rationalized by assuming a high *kinetic* barrier towards isomerization.[21] In line with this notion, pure (*E*)-**17** remained unchanged when exposed to high loading of catalyst **16** (up to 50 mol%) under an ethylene atmosphere.

Flash chromatography allowed for the isolation of the desired product (*E*)-**17** in pure form from the crude reaction mixture, whereas analytical samples of the (*Z*)-isomer could only be



Scheme 3 *Reagents and conditions*: [a] see text; [b] CAN, MeCN/H_2O, 0 °C, 67%; [c] BBr_3, CH_2Cl_2, −78 °C → 0 °C, 40%.

obtained by preparative HPLC.§ With the desired cycloalkene in hand, the completion of the synthesis was straightforward, comprising an oxidative cleavage of the PMP-ether with CAN[22] followed by demethylation using BBr_3 in CH_2Cl_2 at −78 °C. While the spectroscopic data of synthetic aspercyclide C (**1**) are in excellent agreement with those reported in the literature,§ the optical rotation of our sample ($[\alpha]_D^{23}$ +229.7 (*c* 0.39, MeOH)) is significantly higher than that given in ref. 4 ($[\alpha]_D^{23}$ +122.5 (*c* 0.4, MeOH)). Despite this discrepancy in magnitude, the match of all other data leaves no doubt that the constitution and stereochemistry of **1** have previously been correctly assigned by spectroscopic means.

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Notes and references

‡ Calculations were carried out using PC Spartan '02, Wavefunction Inc. Conformational analyses were performed with an MMFF force field, single point energies were calculated (HF-3-21G*) for the minimum energy conformer of each stereoisomer.

§ Physical and spectroscopic data: A compilation of the data of the metathesis products (*E*)-**17** and (*Z*)-**17** as well as copies of their NMR spectra can be found in the Supporting Information. Physical and spectroscopic data of aspercyclide C (**1**): mp 188–189 °C; $[\alpha]^{23}_D$ = +229.7° (*c* 0.39, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (t, J = 8.0 Hz, 1 H), 7.07 (t, J = 7.9 Hz, 1 H), 6.98 (dd, J = 8.1 Hz, J = 1.6 Hz, 1 H), 6.90 (d, J = 7.6 Hz, 1 H), 6.68 (bd, J = 7.6 Hz, 1 H), 6.65 (d, J = 8.4 Hz, 1 H), 6.27 (d, J = 15.9 Hz, 1 H), 5.99 (dd, J = 15.9 Hz, J = 9.5 Hz, 1 H), 5.22 (dt, J = 9.3 Hz, J = 2.0 Hz, 1 H), 4.04 (t, J = 9.3 Hz, 1 H), 2.37 (s, 3 H), 2.07 (m, 1 H), 1.72–1.65 (m, 3 H), 1.55 (m, 2 H), 1.37 (m, 4 H), 0.93 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 153.7, 150.0, 141.9, 137.5, 135.4, 132.5, 130.3, 128.1, 126.7, 126.0, 125.0, 121.4, 115.5, 114.7, 77.5, 77.0, 31.6, 31.6, 25.3, 22.5, 19.5, 14.0; IR (film): 3248, 2957, 2924, 2859, 1709, 1588, 1458, 1267, 963, 763; MS (EI) *m*/*z* (rel. intensity): 382 ([M^+], 1), 282 (50), 264 (29), 254 (22), 253 (100), 236 (30), 211 (10), 135 (19); HR-MS (EI) *calcd*.: 405.1675 [$(M + Na)^+$]; *found*: 405.1672; elemental analysis *calcd*. for $C_{23}H_{26}O_5$: C 72.23, H 6.85; *found*: C 72.18, H 6.73%. For copies of the NMR spectra of **1**, see Supporting Information.†

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