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Natural Products Synthesis

Total Synthesis of Isoxeniolide A**

*Leo Betschart and Karl-Heinz Altmann**

Abstract: Isoxeniolide A is a highly strained xenicane diterpenoid of marine origin. This natural product is representative for a subfamily of xenicanes incorporating an allylic hydroxy group in the nine-membered ring; members of this xenicane subfamily so far have not been targeted by total synthesis. Herein, we describe the first asymmetric total synthesis of isoxeniolide A. Key to forming the challenging *E*-configured cyclononene ring was a diastereoselective intramolecular Nozaki–Hiyama–Kishi reaction. Other important transformations include an enzymatic desymmetrization for absolute stereocontrol, a diastereoselective cuprate addition and the use of a bifunctional vinyl silane building block. Our strategy also permits access to the enantiomer of the natural product and holds potential to access a multitude of xenicane natural products and analogs for structure–activity relationship studies.

Introduction

Natural products represent a highly prolific source of potential drug candidates and of lead structures for drug discovery, and they can serve as unique molecular tools for cell biology and biomedical research.[1–4] So far, most natural products that have been explored in these contexts are derived from terrestrial plants or bacteria; in comparison, compounds produced by marine organisms have featured less prominently in drug discovery and chemical biology,[5,6] but in many cases have been shown to cover chemical space and display bioactivities that extend beyond those associated with terrestrial secondary metabolites.[7–9] As a case in point, the xenicane family of marine diterpenoids[10] is based on a rare cyclononene-containing scaffold (Figure 1) that can be oxidatively modified in various ways, most frequently leading to bicyclic systems (for general reviews, see Refs. [11,12]). In many cases, these structures are highly strained, due to the presence of an *E*-configured C7–C8 double bond in the nine-membered ring. To date, around 200 xenicane-type diterpenoids have been isolated, mostly from soft corals or brown algae, with more than 90 exhibiting distinct biological activities that could be relevant for drug discovery.[13] Physiologically, these compounds are assumed to be part of the producing organisms' chemical self-defense systems.[14–17]

Isoxeniolide A (**1**; Figure 1) was first isolated from *Xenia novaebritanniae* by Braekman et al. in 1979[18] and then re-isolated from *Xenia* sp. by Anta et al. in 2002[19] and from *Asterospicularia laurae* by Lin et al. in 2021.[20] The biological activity of **1** has been assessed only to a very limited extent. Anta *et al.* have reported the IC_{50} values for growth inhibition of 4 cancer lines to be ">1 μg/mL",[19] while Lin et al. found the compound to be inactive against 3 cancer cell lines at a concentration of 100 μM.[20] Isoxeniolide A (**1**) is archetypical for a number of complex, oxygenated xenicane natural products, for example, xeniolide A,[21] hydroxyxeniolide F,[19] xeniaoxolane,[22] or some of the asterolaurins;[23] and several more.[18,19,24–28]

Until very recently total syntheses of xenicane-type diterpenoids had been reported only for four family members, namely antheliolide A (**2**; Corey, 2006),[29] coraxeniolide A (**3**; Leumann, 2000;[30] Corey, 2006[31]), blumiolide C (**4**; Altmann, 2008)[32] and 4-hydroxydictyolactone (**5**; Williams, 2009)[33] (Figure 1).[34][35] Earlier this year, this list has been extended notably by the elegant work of Magauer and co-workers on the total synthesis of waixenicin A (**6**; together with xeniafaraunol A),[36,37] with waixenicin A (**6**) being a nM inhibitor of the transient receptor membrane melastatin (TRPM) 7 channel.[38] In all cases, the major challenge was the construction of the strained nine-membered ring, which was accomplished through different approaches; for antheliolide A (**2**), coraxeniolide A (**3**), blumiolide C (**4**), and waixenicin (**6**) additional difficulties arose in conjunction with the installation of the exocyclic C11–C19 double bond (see below).

In comparison with all other xeniolides for which total syntheses have been described, isoxeniolide A (**1**) features an intriguing hydroxylated allylic stereocenter at C9, a structural element that is not readily accessible by the previously developed synthetic routes.[12,34] In this paper, we describe the first total synthesis of isoxeniolide A (**1**). The strategy that we have developed for **1** can serve as a general blueprint for the synthesis of other *E*-configured 9-hydrox-

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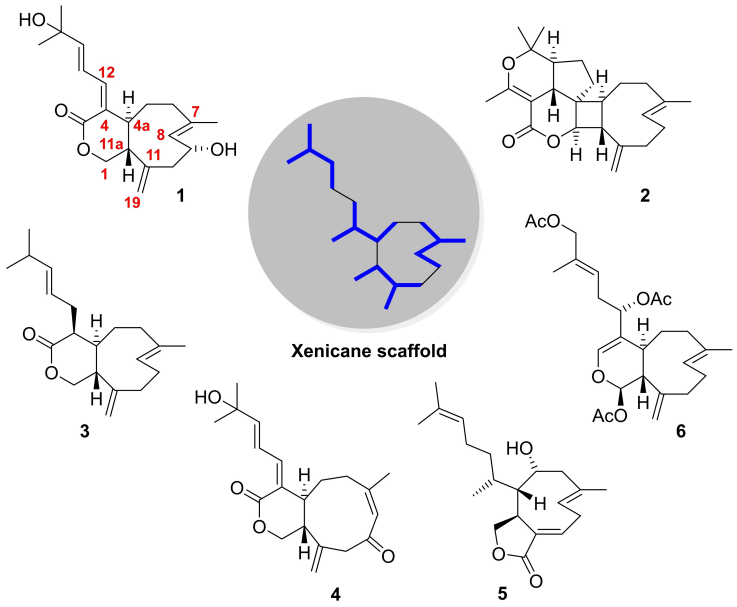


Figure 1. Structure of the xenicane scaffold and of xenicane family members for which total syntheses have been reported: antheliolide A (**2**), coraxeniolide A (**3**), blumiolide C (**4**), 4-hydroxydictyolactone (**5**), and waixenicin A (**6**; see text for details).

yxenicanes; at the same time, it allows for straightforward modification of the nine-membered ring system, should this be desired in the course of structure–activity relationship (SAR) studies.

Results and Discussion

Synthetic planning

As we wanted to develop a total synthesis of **1** that could also serve as a platform for eventual SAR studies around its oxabicyclo[7.4.0]tridecene core structure, one of the preconditions that directed our synthetic planning was the late stage incorporation of the C4 side chain (see Figure 1 for atom numbering). Such an approach would give efficient access to side-chain-modified variants of **1** from a common advanced precursor. A second critical question pertained to the formation of the C11–C19 double bond, where we wanted to circumvent the difficulties that we had encountered in our total synthesis of blumiolide C (**4**).[32] In that case, all attempts at the direct olefination of the C11 ketone intermediate **7** had failed (Figure 2A); while the installation of the C11–C19 double bond was possible eventually by elimination across the C11–C19 bond, this could only be achieved after prior reduction of the lactone moiety to an acetal (Figure 2B). At the lactone stage the formation of an endocyclic double bond between C10 and C11 prevailed.[32]

In contrast to our experience with **7**, Magauer and coworkers have recently reported the olefination of ketone **11** as part of their synthesis of waixenicin A (Figure 2C).[36,37] However, extensive screening and optimization were re-

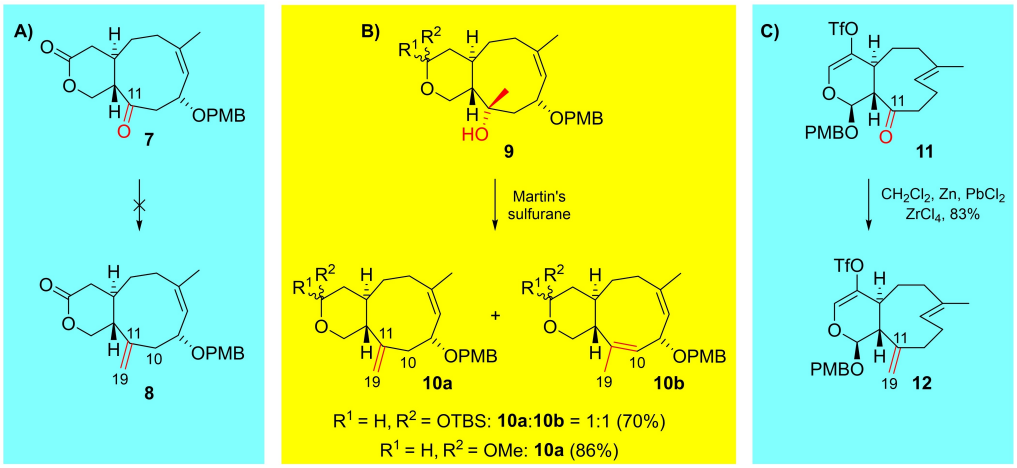


Figure 2. Installation of the C11–C19 double bond en route to A,B) blumiolide C (**4**)[32] and C) waixenicin (**6**).[36,37] PMB = *p*-methoxybenzyl.

quired, in order to identify conditions that would enable this transformation.

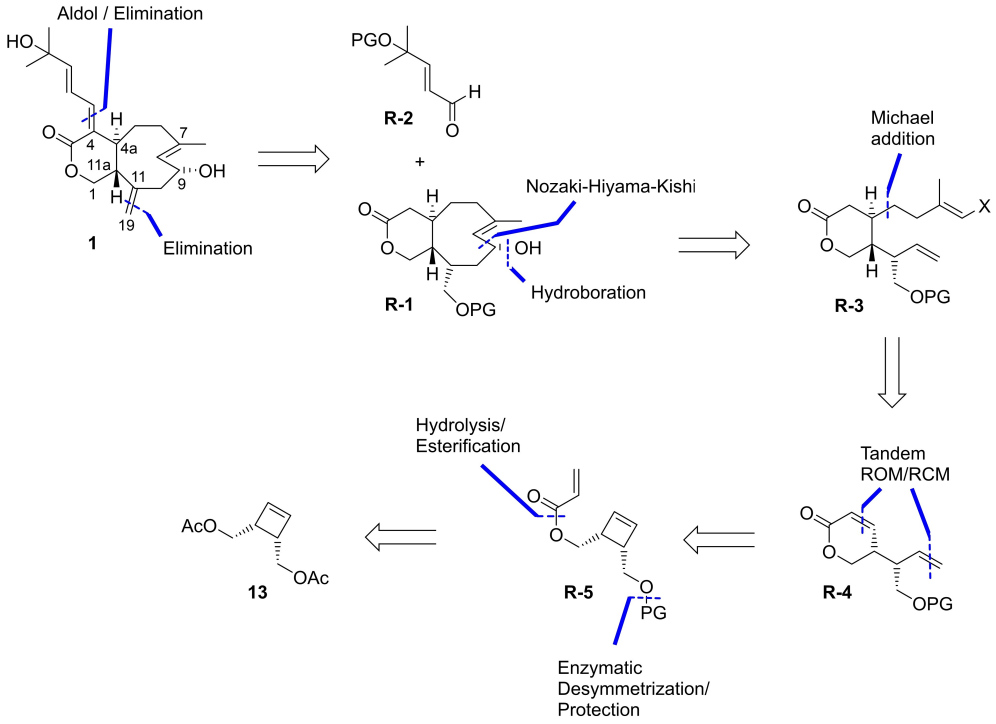
With the above provisions in mind, the initial disconnections in our retrosynthesis of isoxeniolide A (**1**) led us to protected bicyclic lactone **R-1** as a key intermediate, through (1) an aldol transform with an appropriately protected aldehyde **R-2** for introduction of the C4 side chain and (2) an elimination transform for the installation of the C11–C19 exocyclic methylene group (Scheme 1). Further disconnection of **R-1** at the C8–C9 bond then led to vinyl (pseudo)halides of type **R-3** as possible synthons for the construction of the *E* nonene ring through hydroboration/oxidation of the C10–C9 homoallylic double bond (isoxeniolide numbering, see Figure 1), followed by an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction. A limited number of NHK-based cyclizations to form nine-membered rings have been described in the literature, including vinyl iodides giving rise to rings with the reacting vinyl double bond located either in an exocyclic or endocyclic position.[39]

For the latter type of substrates, Magauer has reported the cyclization of a disubstituted *Z* vinyl iodide in 28 % yield, in the context of studies towards the synthesis of cornexitin.[40] To the best of our knowledge, the only examples for the cyclization of *E*-configured vinyl (pseudo)halides have been described by Procter and co-workers[41] as well as Takao, Tadano and co-workers[42] for the formation of the nine-membered ring in pestalotiopsin A through intramolecular NHK reactions in yields between 45 % and 92 %.[43] As in Magauer's case,[40] these latter cyclizations were found to be highly stereoselective; while this was encouraging, it needs be noted that the cyclization precursors in the pestalotiopsin case incorporated a stereocenter adjacent to the aldehyde group, which may have been beneficial for the stereochemical outcome of the cyclization. It was thus uncertain at the planning stage, if the conversion of vinyl (pseudo)halides of type **R-3** into carbocycle **R-1** would be stereoselective and, if so, to what degree and in favor of which isomer. Should the selectivity be unsatisfactory, we planned to investigate the use of enantioselective catalysts that have been reported for NHK reactions.[44]

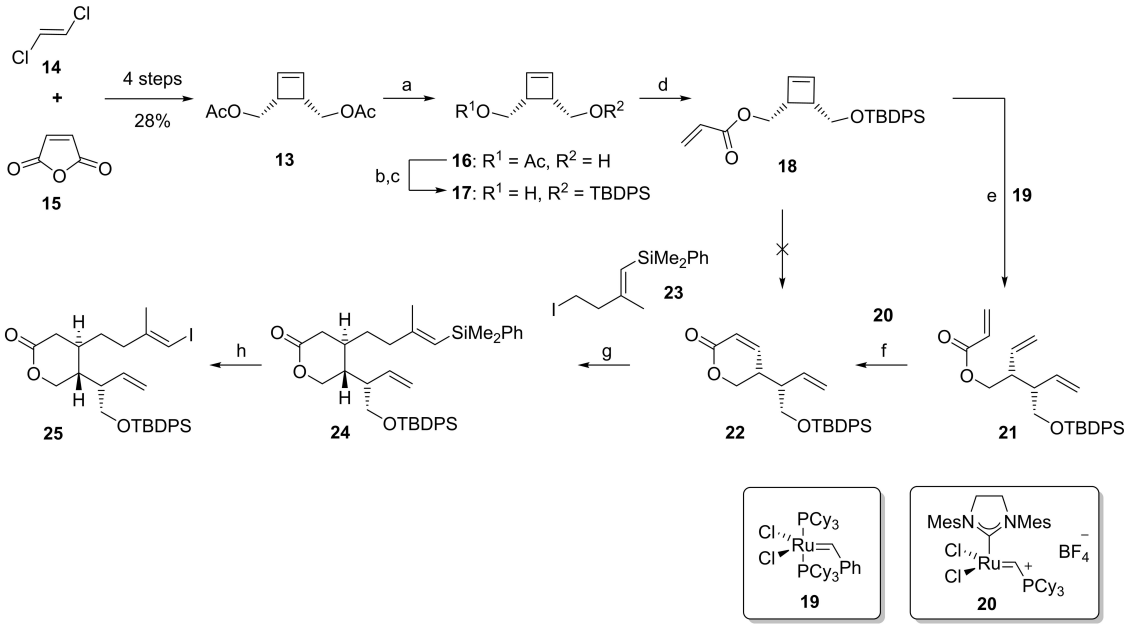
The stereocenter at C4a was to be installed by exploiting cyclic stereocontrol in the conjugate addition of an organocuprate reagent to α,β-unsaturated lactone **R-4**. The former also contains the required functional handle for further elaboration. The requisite lactone **R-4** was envisioned to be accessible through a cascade ring-opening metathesis (ROM)/ring-closing metathesis (RCM) reaction[45–48] of chiral cyclobutene **R-5**; the latter was traced back to the achiral cyclobutene **13**, which had been reported to undergo enantioselective desymmetrization.[49]

Assembly of the carbon framework of the core structure

As depicted in Scheme 2, the ultimate starting materials for the synthesis of the chiral cyclobutene precursor **18** (i.e. **R-5** with PG=TBDPS) for the projected ROM-RCM cascade reaction were *E*-1,2-dichloroethene (**14**) and maleic anhydride (**15**), which were elaborated into the known diacetate **13**[50] in 4 steps and 28 % overall yield. The latter was then desymmetrized with *Pseudomonas fluorescens* lipase as described by Harvey and Crout,[49] to furnish **16** in 61 %–82 % yield with ee's of 90 %–94 %. (For a detailed investigation of the conditions for this reaction see the SI).



Scheme 1. Retrosynthesis of isoxeniolide A (**1**). PG = protecting group; X=I, OTf, SiR_3 or SnR_3.



Scheme 2. a) *Pseudomonas fluorescens* lipase, buffer pH 7 (67 mM), neutralization with NaOH (1 M), room temperature, 61–82%, 90–94% ee; b) TBDPSCl (1.1 equiv), ImH (3.7 equiv), DMF, room temperature, 32 h, 97%; c) K_2CO_3 (0.2 equiv), MeOH, room temperature, 5 h, quant.; d) acryloyl chloride (2 equiv), DIPEA (3.5 equiv), DMAP (0.2 equiv), CH_2Cl_2, −78 °C, 20 min; e) **19** (4 mol%), ethylene, room temperature, CH_2Cl_2, 26 h; f) **20** (12 mol%), CH_2Cl_2, 40 °C, 44 h, 46% (3 steps) and 4% (3 steps) recovery of **21**; g) i) *t*-BuLi (3.5 equiv), **23** (1.8 equiv), Et_2O, −78 °C, 2 h; ii) LiCu(thienyl)CN (1.9 equiv), −78 °C, 8 min, 0 °C, 2 h; iii) **22** (1 equiv), −78→−60 °C over 1 h, 0 °C, 20 min, 79%; h) NIS (1.15 equiv), Ag_2CO_3 (0.3 equiv), HFIP, 0 °C, 10 min, 88%, (99% BRSM). BRSM = based on recovered starting material, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylamino pyridine, DMF = *N*,*N*-dimethylformamide, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, NIS = N-iodosuccinimide, TBDPS = *tert*-butyldiphenylsilyl.

Alcohol **16** was then elaborated into acrylate ester **18** by TBDPS-protection, methanolysis of the acetate ester with K_2CO_3/MeOH and reaction of the ensuing primary alcohol with acryloyl chloride in high overall yield (around 75%). Acrylate **18** was found to be prone to polymerization when evaporated to dryness and, thus, was usually isolated as a solution in hexane directly after flash chromatography.

With sufficient quantities of **18** accessible, the stage was set for the projected tandem ROM/RCM reaction to obtain enoate **22**. While a small scale catalyst screen with racemic **18** (without isolation of products) had indicated the Hoveyda-Grubbs (HG) I catalyst[51] in CH_2Cl_2 to affect the desired transformation of **18** into **22** cleanly, these findings turned out not to be reproducible on a preparatively useful scale and only traces of **22** were isolated. Although the material obtained appeared homogeneous on TLC, it contained additional impurities as revealed by ^{1}H NMR. Similar observations were made with Grubbs (G) I catalyst (**19**).

Based on work by Snapper,[47,48] we then investigated the effect of ethylene as an additive in the ROM, which revealed high-yielding conversion of **18** into triene **21** with both the HG I as well as the G I catalyst, without subsequent ring-closure to **22**. Under optimized conditions, yields for the ring-opening metathesis were in the range of 80% - 90%; however, as for cyclobutene **18**, triene **21** was prone to polymerization and for reactions conducted on larger scale, the compound was isolated only as a solution in hexanes. RCM with **21** was then best affected with Piers-Grubbs (PG) II catalyst (**20**);[52,53] heating of solution of **21** in CH_2Cl_2/hexane 10:1.5 with 12 mol-% of **20** to 40 °C for 3 days gave lactone **22** in 46% yield for the three-step sequence from TBDPS-ether **17**. A number of other commonly used ruthenium-based metathesis catalysts (Grubbs and Hoveyda-Grubbs type)[51] were investigated for the ring-closing reaction, but all of them suffered from low conversion and/or sluggish reaction rates. It is noteworthy that a temperature of 40 °C was required for the cyclization of **21**, even with the fast-initiating catalyst **20**.[52] At this temperature, we found decomposition of the catalyst to be a significant issue, which could be partially mitigated by portion-wise addition of the catalyst in minimum portions of 2.5%. The thermal stability of catalyst **20** has also been discussed by Piers and co-workers.[54] In contrast to **18** and **21**, lactone **22** proved to be bench-stable for several weeks.

The conversion of **22** into vinyl iodide **25** then entailed the 1,4-addition of a higher-order Lipshutz cuprate[55,56] derived from iodide **23**,[57] which gave **24** as a single stereoisomer in 79% yield. While **24** obtained in this way was generally contaminated with a decomposition product of **23**, this impurity was easily removed after the next step by simple evaporation. Treatment of **24** with iodine gave no conversion, but the use of *N*-iodosuccinimide (NIS) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[58] with silver carbonate as an additive[59] furnished vinyl iodide **25** in excellent yield.

Aldehyde formation and NHK cyclization

In order to establish suitable conditions for the hydroboration of the homoallylic double bond in **25**, preliminary experiments were carried out with the isomeric mixture of vinyl iodides **26** (Figure 3).[60]

To our surprise, the reaction of this compound with 9-borabicyclo[3.3.1]nonane (9-BBN) in THF was very sluggish and required heating to 70 °C to induce conversion. However, the only product isolated from this reaction in 36 % yield (albeit impure) was not the desired primary alcohol; rather, the analytical data pointed to the reduction of the lactone moiety to a diol, without conversion of the double bond. When lactone **26** was converted into methyl acetal **27** (Figure 3), which additionally contains a sterically less demanding TBS-ether group in proximity to the double bond, no reaction was observed under any of the hydroboration conditions investigated. These initial observations prompted a change in the hydroxy protecting group from TBDPS to PMB through TBDPS-ether cleavage with HF·pyridine followed by the TMSOTf-catalyzed alkylation of the free alcohol with *p*-methoxybenzyl trichloroacetimidate, to furnish **28** in 50 % overall yield (Scheme 3).

The direct use of the PMB-protecting group already in the earlier stages of the synthesis was prohibitive, as triene **36** (Figure 3) had proven to be a poor substrate for RCM with a whole series of Ru-based metathesis catalysts (G–I, G-II, G-III, HG–I, HG-II, PG-II).[51] In all cases, conversion into the desired lactone was < 15 % or did not occur at all (see the SI).

When PMB-protected lactone **28** was treated with 9-BBN (1.1 equiv) in THF, the only product obtained after oxidation was the corresponding lactol (26 % yield) together with 19 % of recovered starting material. Gratifyingly,

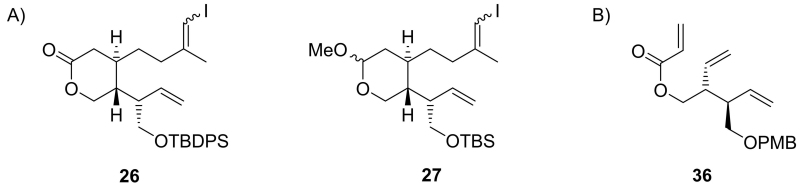
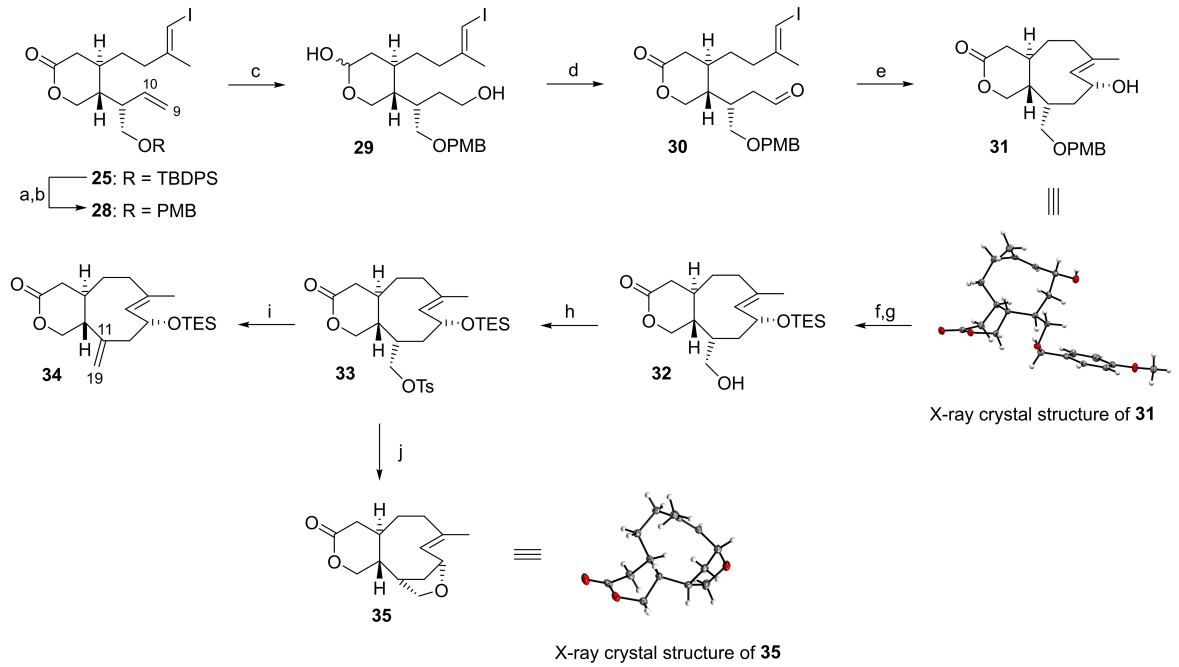


Figure 3. A) Substrates for the evaluation of hydroboration conditions. B) PMB-protected triene that did not undergo RCM (see text for details). TBS = *tert*-butyldimethylsilyl.



Scheme 3. a) HF·py (4.2 equiv. based on HF), THF, room temperature, 18 h, 82 %; b) $PMBO(NH)CCCl_3$ (1.50 equiv), TMSOTf (0.05 equiv), CH_2Cl_2, −78 °C, 40 min, 61 %; c) i) 9-BBN (2.25 equiv), THF, −78 °C, 2.5 h; ii) MeOH (80 equiv), NaOH (2.25 equiv), 0 °C→rt, 30 min; iii) H_2O_2 (6.6 equiv), 0 °C→rt, 30 min, 81 %; d) TPAP (0.1 equiv), NMO (5 equiv), 4 Å molecular sieves, CH_2Cl_2, room temperature, 70 %; e) $CrCl_2$ (7.5 equiv), $NiCl_2$ (0.06 equiv), DMSO, room temperature, 71 %; f) TESCl (1.1 equiv), ImH (3.7 equiv), CH_2Cl_2, 4 h, 85 %; g) DDQ (2.14 equiv), buffer pH 7, CH_2Cl_2, 0 °C, 5 min, room temperature, 1 h 45 min, 93 %; h) TsCl (3 equiv), NEt_3 (6 equiv), DMAP (0.5 equiv), CH_2Cl_2, room temperature, 20 h, 89 %; i) NaI (5 equiv), DBU (3 equiv), DME, 90 °C, 3 h, 78 %; j) same conditions as in (i) but with **33** of only 66 % purity, 50 % (see text for details). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethyl sulfoxide, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

employing 2.25 equivalents of 9-BBN gave the hydroboration product of the lactol, that is, **29**, in 81 % yield (Scheme 3). For the reaction to deliver **29** in high yield reproducibly, it was crucial that the starting lactone **28** was azeotropically dried by evaporation with benzene directly before use and that both MeOH and NaOH were added simultaneously in the quenching step. When these measures were omitted (and the reaction was quenched solely with MeOH and the NaOH was added to the quenched solution only later), we observed extensive formation of the methyl acetal of **29**.

A number of different standard oxidants were then screened for the double oxidation of **29** to the desired lactone-aldehyde **30** (including DMP, unbuffered[61] or in the presence of additives,[62] PCC, PDC, TEMPO/DAIB,[63,64] alone or in combination with $Yb(OTf)_3$[65]). From this screen, the Ley-Griffith oxidation,[66,67] which uses catalytic tetrapropylammonium perruthenate (TPAP) in combination with *N*-methylmorpholine *N*-oxide (NMO) as the terminal oxidant, emerged as the most efficient method by far for the direct conversion of **29** into **30**. Using 5 equiv. of NMO and 10 mol-% of TPAP, **29** was converted into **30** in 15 min; as the latter was found to be unstable on silica gel, purification only involved filtration through a plug of silica (to remove an apolar impurity), which gave **30** in almost pure form in yields between 65 % and 70 %. This material was then immediately used in the next step.

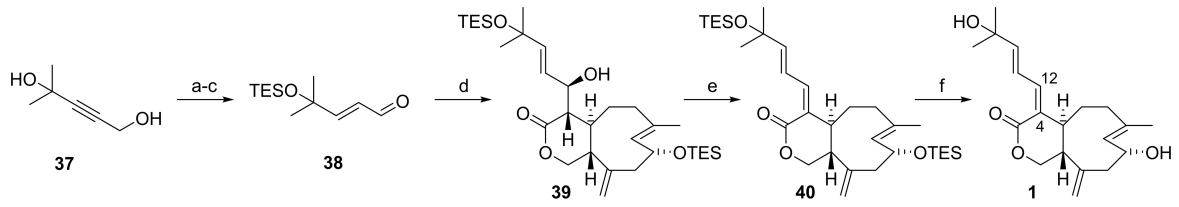
The formation of the nine-membered ring through NHK cyclization of **30** was surprisingly smooth, furnishing the desired nonenol **31** as a single stereoisomer in yields between 57 % and 71 % (Scheme 3). The relative configuration of the cyclization product was initially deduced from extensive NOE measurements and subsequently confirmed by X-ray crystallography (Scheme 3).[68,69] Under optimized conditions, the reaction could be carried out on a 100 mg scale or larger at 20 mM concentration with 7.5 equivalents of $CrCl_2$ and 0.06 equivalents of $NiCl_2$. Only slow decomposition of **30** without any conversion to product was observed under the catalytic NHK conditions elaborated by Fürstner.[70,71]

To enable the installation of the critical C11–C19 double bond, the cyclization product **31** was elaborated into tosylate **33** by TES-protection of the allylic hydroxy group (TESCl), cleavage of the PMB-ether with DDQ and conversion of the ensuing free hydroxy group with tosyl chloride in 70 % overall yield. Employing Maier's one-pot tandem Finkelstein/elimination methodology,[72] tosylate **33** could then be converted into the desired olefin **34** in high yield (78 %). To achieve reproducible results in this step, rigorously anhydrous conditions and the use of freshly distilled DBU proved to be crucial. Moreover, a reaction time of at least 2 h, preferably 3 h was important; while the intermediate iodide is completely formed within 1 h, additional time is required for full conversion to **34**. Finally, it is important to note that tosylate **33** proved to be highly prone to decomposition and had to be used immediately after its preparation. When partly decomposed **33** (ca. 66 % purity based on ^{1}H NMR analysis; with the remainder of the compound having decomposed into unidentified products) was submitted to the elimination conditions, the major product obtained (in 50 % yield) was bicycle **35** (Scheme 3), whose structure was secured by X-ray crystallography. The pathway to this product likely involves loss of the TES-protecting group (which may be triggered by the decomposition products), followed by an S_N2-attack of the allylic hydroxy group on a C19 tosylate or iodide. Attempts to effect olefin formation by Grieco-Sharpless elimination[73,74] (with either Bu_3P[73,74] or Me_3P[75]) at the stage of the free alcohol **32** were completely unsuccessful, as was the direct formation of the iodide under Appel conditions. No conversion of **32** was observed.

Side chain attachment and completion of the total synthesis

With access to the isoxeniolide A core structure established on a multiple 100 mg scale, the completion of the total synthesis finally required the stereoselective attachment of the C4 side chain. As the hydroxy group on the core structure was protected as a TES-ether, TES-protected γ-hydroxy aldehyde **38** (Scheme 4) appeared to be a sensible coupling partner for the projected aldol condensation with lactone **34** (see Scheme 1). The former was prepared in three steps from diol **37**[76] by *E*-selective reduction of the triple bond with $LiAlH_4$,[77] followed by double TES-protection (TESCl) and direct oxidation of the primary TES-ether under Swern conditions[78] in 49 % overall yield.

Reaction of **38** with the Li-enolate of lactone **34** at −78 °C to −10 °C gave a single aldol product in 29 % yield, which was tentatively assigned structure **39**, that is, as the 4*S*, 12*S* diastereoisomer;[79] in addition 42 % of **34** were recovered from the reaction unchanged. No efforts have



Scheme 4. a) $LiAlH_4$ (4 equiv), THF, 0 °C, 15 min, warmed to room temperature, 45 min, 73 %; b) TESCl (3 equiv), ImH (4.6 equiv), DMAP (0.2 equiv), CH_2Cl_2, room temperature, 1 h 20 min, 96 %; c) $(COCl)_2$ (4.4 equiv), DMSO (10 equiv), Et_3N (20 equiv), CH_2Cl_2, −78 °C→rt, 1 h, 70 %; d) **34**, LiHMDS (2.9 equiv), THF, −78 °C, 1 h, then **38** (1.5 equiv), 2 h, −78→−10 °C over 20 min, 29 %, 42 % recovery of **34**; e) EDCI (5 equiv), $CuCl_2$ (cat.), PhMe, 80 °C, 26 min, 76 %; f) $Et_3N{\cdot}3HF$ (9 equiv), THF, room temperature, 2 days, 80 %.

been made at this point to improve the yield of the aldol reaction. Employing the Ohmizu[80,81] variant of the Corey dehydration,[82,83] the aldol product was then transformed into the desired olefin **40** with EDCI/$CuCl_2$ in 76 % yield. The use of EDCI as the free base was critical for the success of the reaction, otherwise no conversion took place. The configuration of the C4–C12 double bond was assigned based on the comparison of NMR chemical shifts and coupling constants with the corresponding literature values for xeniolide A and isoxeniolide A (**1**).[18]

Global deprotection of **40** with $Et_3N \cdot 3HF$ in THF gave isoxeniolide A (**1**) in 80 % yield. While cleavage of the first TES-ether group was complete within 2 h at ambient temperature, a total reaction time of 2 days was required for full deprotection. The ^1H- and ^{13}C NMR data for synthetic **1** were in full agreement with those reported by Braekman and co-workers for natural isoxeniolide A.[18] Likewise, the specific rotation of synthetic **1** ($[\alpha]^{20}_D = +19.22°$ ($c = 0.385$, MeOH)) displayed the same sign as the one obtained for natural isoxeniolide A, although it was lower in magnitude than the literature value ($[\alpha] = +50°$ ($c = 0.655$, MeOH)).[18] The reasons for this discrepancy are not clear.

Conclusion

Our successful total synthesis of isoxeniolide A (**1**) represents the first synthesis of a xenicane-type natural product bearing an allylic hydroxy group in the nine-membered ring. The key step in the synthesis was the surprisingly facile, efficient formation of a cyclononene ring in an intramolecular NHK reaction. Other enabling transformations include a challenging ROM/RCM sequence, a diastereoselective cuprate addition, an efficient Ley-Griffith oxidation and the installation of the exocyclic C11–C19 double bond from a C19 tosylate. Enantiocontrol in the synthesis was based on the enzymatic desymmetrization of cyclobutene **13**; our approach thus holds the potential to access the enantiomeric series of xenicanes, which originate from brown algae.[12] While several hundred milligrams of key intermediate **34** could be prepared, the C4 side chain attachment step still needs to be optimized. Notwithstanding this (current) shortcoming, the modularity of our synthetic strategy allows for introduction of a number of potential modifications of both the xenicane core as well as the C4 side chain.

Author Contributions

L.B.: Conceptualization; methodology; formal analysis; investigation; writing original draft; review & editing K.-H.A.: Conceptualization; formal analysis; writing, review & editing; supervision.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

All data are available from the authors upon request. Supporting Information and chemical compound information are available along with the online version of the paper.

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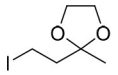
[1] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2020**, *83*, 770–803.
[2] S. S. Bharate, S. Mignani, R. A. Vishwakarma, *J. Med. Chem.* **2018**, *61*, 10345–10374.
[3] E. Patridge, P. Gareiss, M. S. Kinch, D. Hoyer, *Drug Discovery Today* **2016**, *21*, 204–207.
[4] M. Butler, A. A. B. Robertson, M. A. Cooper, *Nat. Prod. Rep.* **2014**, *31*, 1612–1661.
[5] U. Lindequist, *Biomol. Ther.* **2016**, *24*, 561–571.
[6] W. H. Gerwick, B. S. Moore, *Chem. Biol.* **2012**, *19*, 85–98.
[7] C. R. Pye, M. J. Bertin, R. S. Lokey, W. H. Gerwick, R. G. Linington, *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 5601–5606.
[8] Y. Hu, J. Chen, G. Hu, J. Yu, X. Zhu, Y. Lin, S. Chen, J. Yuan, *Mar. Drugs* **2015**, *13*, 202–221.
[9] R. Montaser, H. Luesch, *Future Med. Chem.* **2011**, *3*, 1475–1489.
[10] D. J. Vanderah, P. A. Steudler, L. S. Ciereszko, F. J. Schmitz, J. D. Ekstrand, D. Van Der Helm, *J. Am. Chem. Soc.* **1977**, *99*, 5780–5784.
[11] S.-Y. Ng, C.-S. Phan, T. Ishii, T. Kamada, T. Hamada, C. S. Vairappan, *Molecules* **2020**, *25*, 5386.
[12] L. Betschart, K.-H. Altmann, *Curr. Pharm. Des.* **2015**, *21*, 5467–5488.
[13] This estimate is based on the numbers reported in Refs. [11] and [12] and from reports on the isolation of new xenicane-type diterpenoids published since 2020.
[14] G. Cronin, M. E. Hay, *Bot. Mar.* **1996**, *39*, 395–399.
[15] D. Kelman, Y. Kashman, E. Rosenberg, A. Kushmaro, Y. Loya, *Mar. Biol.* **2006**, *149*, 357–363.
[16] D. Kelman, Y. Kashman, R. T. Hill, E. Rosenberg, Y. Loya, *Pure Appl. Chem.* **2009**, *81*, 1113–1121.
[17] E. Andrianasolo, R. Lutz, P. Falkowski, in *Studies in Natural Products Chemistry* (Ed.: A. Rahman), Elsevier B. V., Oxford, **2012**, pp. 43–66.

[18] J. C. Braekman, D. Daloze, B. Tursch, J. P. Declercq, G. Germain, M. van Meerssche, *Bull. Soc. Chim. Belg.* **1979**, *88*, 71–77.
[19] C. Anta, N. González, G. Santafé, J. Rodríguez, C. Jiménez, *J. Nat. Prod.* **2002**, *65*, 766–768.
[20] Y.-C. Lin, Y.-J. Chen, S. R. Chen, W. J. Lien, H.-W. Chang, Y.-L. Yang, C.-C. Liaw, J. H. Su, C. Y. Chen, Y. B. Cheng, *Mar. Drugs* **2021**, *19*, 123.
[21] Y. Kashman, A. Groweiss, *Tetrahedron Lett.* **1978**, *19*, 4833–4836.
[22] H. Miyaoka, H. Mitome, M. Nakano, Y. Yamada, *Tetrahedron* **2000**, *56*, 7737–7740.
[23] Y.-S. Lin, A. Eid Fazary, C.-H. Chen, Y.-H. Kuo, Y.-C. Shen, *Helv. Chim. Acta* **2011**, *94*, 273–281.
[24] H. Miyaoka, M. Nakano, K. Iguchi, Y. Yamada, *Heterocycles* **2003**, *61*, 189–196.
[25] A. Rudi, S. Ketzinel, I. Goldberg, Z. Stein, Y. Kashman, *J. Nat. Prod.* **1995**, *58*, 1581–1586.
[26] S.-K. Wang, M.-J. Huang, C.-Y. Duh, *J. Nat. Prod.* **2006**, *69*, 1411–1416.
[27] B. F. Bowden, B. J. Cusack, A. Dangel, *Mar. Drugs* **2003**, *1*, 18–26.
[28] T. Grkovic, E. L. Whitson, D. C. Rabe, R. S. Gardella, D. P. Bottaro, W. M. Linehan, J. B. McMahon, K. R. Gustafson, T. C. McKee, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2113–2115.
[29] C. S. Mushti, J.-H. Kim, E. J. Corey, *J. Am. Chem. Soc.* **2006**, *128*, 14050–14052.
[30] D. Renneberg, H. Pfander, C. J. Leumann, *J. Org. Chem.* **2000**, *65*, 9069–9079.
[31] O. Larionov, E. J. Corey, *J. Am. Chem. Soc.* **2008**, *130*, 2954–2955.
[32] C. Hamel, E. V. Prusov, J. Gertsch, W. B. Schweizer, K.-H. Altmann, *Angew. Chem. Int. Ed.* **2008**, *47*, 10081–10085.
[33] D. R. Williams, M. J. Walsh, N. A. Miller, *J. Am. Chem. Soc.* **2009**, *131*, 9038–9045.
[34] For a review on the synthesis of xenicane-type diterpenoids, see: T. Huber, L. Weisheit, T. Magauer, *Beilstein J. Org. Chem.* **2015**, *11*, 2521–2539.
[35] It should be noted that *Xenia* diterpenoids of the xeniaphyllan class are based on the same core structure as the plant derived caryophyllans. For the first enantioselective synthesis of β-caryophellene, see Ref. [31].
[36] C. Steinborn, T. Huber, J. Lichtenegger, I. Plangger, K. Wurst, T. Magauer, *J. Am. Chem. Soc.* **2023**, *145*, 11811–11817.
[37] C. Steinborn, T. Huber, J. Lichtenegger, I. Plangger, D. Höfler, S. D. Schnell, L. Weisheit, P. Mayer, K. Wurst, T. Magauer, *Chem. Eur. J.* **2023**, *29*, e202303489.
[38] S. Zierler, G. Yao, Z. Zhang, W. C. Kuo, P. Pörzgen, R. Penner, F. D. Horgen, A. Fleig, *J. Biol. Chem.* **2011**, *286*, 39328–39335.
[39] For a recent review on the synthesis of nine-membered carbocycles, see: T. Huber, R. E. Wildermuth, T. Magauer, *Chem. Eur. J.* **2018**, *24*, 12107–12120.
[40] R. E. Wildermuth, C. Steinborn, D. M. Barber, K. S. Mühlfenzl, M. Kendlbacher, P. Mayer, K. Wurst, T. Magauer, *Chem. Eur. J.* **2021**, *27*, 12181–12189.
[41] T. M. Baker, D. J. Edmonds, D. Hamilton, C. J. O'Brien, D. J. Procter, *Angew. Chem. Int. Ed.* **2008**, *47*, 5631–5633.
[42] K.-I. Takao, N. Hayakawa, R. Yamada, T. Yamaguchi, H. Saegusa, M. Uchida, S. Samejima, K.-I. Tadano, *J. Org. Chem.* **2009**, *74*, 6452–6461.
[43] The cyclized intermediate in Takao's and Tadano's total synthesis of pestalotiopsin could also be elaborated into fuscoatrol A and cytosporolide A: K.-I. TAKAO, S. NOGUCHI, S. SAKAMOTO, M. KIMURA, K. YOSHIDA, K.-I. TADANO, *J. Am. Chem. Soc.* **2015**, *137*, 15971–15977.
[44] For a review on asymmetric NHK reactions, see: Q. Tian, G. Zhang, *Synthesis* **2016**, *48*, 4038–4049.
[45] J. A. Tallarico, M. L. Randall, M. L. Snapper, *Tetrahedron* **1997**, *53*, 16511–16520.
[46] M. L. Randall, M. L. Snapper, *J. Mol. Catal. A* **1998**, *133*, 29–40.
[47] M. Shizuka, M. Snapper, *Synthesis* **2007**, 2397–2403.
[48] B. A. Pandya, M. L. Snapper, *J. Org. Chem.* **2008**, *73*, 3754–3758.
[49] I. Harvey, D. H. G. Crout, *Tetrahedron: Asymmetry* **1993**, *4*, 807–812.
[50] N. Gauvry, C. Comoy, C. Lescop, F. Huet, *Synthesis* **1999**, *4*, 574–576.
[51] For a recent review on Ru-based olefin metathesis see: O. M. Ogba, N. C. Warner, D. J. O'Leary, R. H. Grubbs, *Chem. Soc. Rev.* **2018**, *47*, 4510–4544.
[52] P. E. Romero, W. E. Piers, R. McDonald, *Angew. Chem. Int. Ed.* **2004**, *43*, 6161–6165.
[53] S. R. Dubberley, P. E. Romero, W. E. Piers, R. McDonald, M. Parvez, *Inorg. Chim. Acta* **2006**, *359*, 2658–2664.
[54] E. M. Leitao, W. E. Piers, M. Parvez, *Can. J. Chem.* **2013**, *91*, 935–942.
[55] B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen, K. E. McCarthy, *J. Organomet. Chem.* **1985**, *285*, 437–447.
[56] B. H. Lipshutz, M. Koerner, D. A. Parker, *Tetrahedron Lett.* **1987**, *28*, 945–948.
[57] D. F. Taber, R. S. Bhamidipati, L. Yet, *J. Org. Chem.* **1995**, *60*, 5537–5539.
[58] E. A. Ilardi, C. E. Stivala, A. Zakarian, *Org. Lett.* **2008**, *10*, 1727–1730.
[59] M. Sidera, A. M. Costa, J. Vilarrasa, *Org. Lett.* **2011**, *13*, 4934–4937.
[60] Vinyl iodide **26** was obtained by (non-selective) iodomethylenation of the corresponding ketone precursor. The latter had been prepared *via* 1,4-addition of a cuprate derived from iodide **41** to lactone **22**.



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[61] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156.
[62] A. Rühmann, C. Wentrup, *Tetrahedron* **1994**, *50*, 3785–3796.
[63] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974–6977.
[64] T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, C. J. Forsyth, *Tetrahedron Lett.* **2003**, *44*, 57–59.
[65] J.-M. Vatèle, *Synlett* **2006**, 2055–2058.
[66] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625–1627.
[67] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639–666.
[68] The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under deposition numbers CCDC 1566981 (**31**), CCDC 1566982 (**35**; relative configuration), 1566983 (**35**; absolute configuration), and 1566984 (**S-5**; relative confiduration. See the SI). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures.
[69] We speculate that the high selectivity of the NHK cyclization might arise from metal chelation by the aldehyde carbonyl and the PMB-ether oxygen, so as to place the C11 substituent and the newly formed allylic hydroxy group on the same face of the emerging nine-membered ring. However, this hypothesis needs to be confirmed by detailed computational studies.
[70] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 2533–2534.

[71] A. Fürstner, N. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 12349–12357.
[72] P. Phukan, M. Bauer, M. E. Maier, *Synthesis* **2003**, 1324–1328.
[73] K. B. Sharpless, M. W. Young, *J. Org. Chem.* **1975**, *40*, 947–949.
[74] P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485–1486.
[75] T. Tsuruda, M. Ebine, A. Umeda, T. Oishi, *J. Org. Chem.* **2015**, *80*, 859–871.
[76] M. S. Newman, W. S. Fones, W. T. Booth, *J. Am. Chem. Soc.* **1945**, *67*, 1053–1054.
[77] L. Grigorjeva, A. Jirgensons, *Eur. J. Org. Chem.* **2012**, *2012*, 5307–5316.
[78] A. Rodríguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1999**, *40*, 5161–5164.
[79] The stereochemical assigment of the aldol product as **39** was based on the following logic: (1) Aldehyde **38** is expected to approach the enolate from the more accessible face. This stereochemical bias was also observed for related systems in Refs. [29-32] (2) The Corey/Ohmizu dehydration is a *syn* elimination. Assuming (1) to be correct, which is highly likely, in order to account for the geometry of the C4-C12 double bond in **40**, the C12-hydroxy group in the aldol product must then have the configuration as in **39**.
[80] H. Sai, H. Ohmizu, *Tetrahedron Lett.* **1999**, *40*, 5019–5022.
[81] H. Sai, T. Ogiku, H. Ohmizu, *Tetrahedron* **2007**, *63*, 10345–10353.
[82] E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, R. E. K. Winter, *J. Am. Chem. Soc.* **1968**, *90*, 3245–3247.
[83] E. J. Corey, M. A. Letavic, *J. Am. Chem. Soc.* **1995**, *117*, 9616–9617.

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