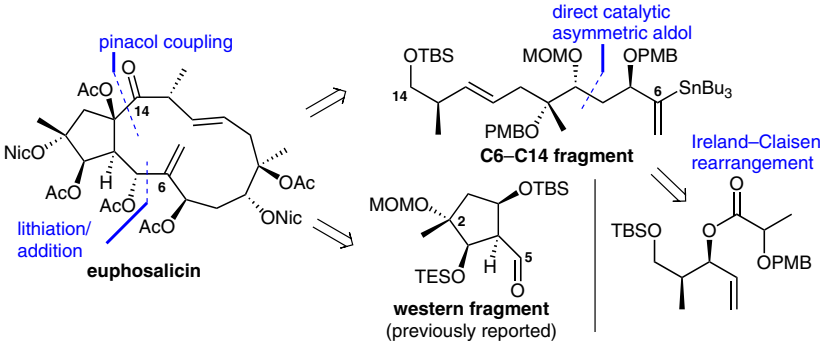
Synlett U. Rinner et al. Letter

Synthesis of the C6–C14 Fragment of Euphosalicin

Christian Aichinger
Johann Mulzer
Uwe Rinner*[1]

Institute of Organic Chemistry, University of Vienna, Währinger Straße 38, 1090 Wien, Austria
uwe.rinner@jku.at



Received: 09.04.2015
Accepted after revision: 07.05.2015
Published online: 19.06.2015
DOI: 10.1055/s-0034-1380422; Art ID: st-2015-b0256-l

Abstract The synthesis of the C6–C14 fragment of euphosalicin, a highly oxygenated modified jatrophane diterpene, is described. Key steps in the preparation of this versatile intermediate are an Ireland–Claisen rearrangement and a Shibasaki direct asymmetric aldol reaction.

Key words natural products, total synthesis, aldol reaction, rearrangement, hydrostannation

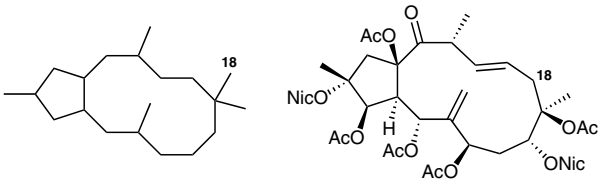


Figure 1 Formal incorporation of the jatrophane C18 methyl group gives the euphosalicin skeleton

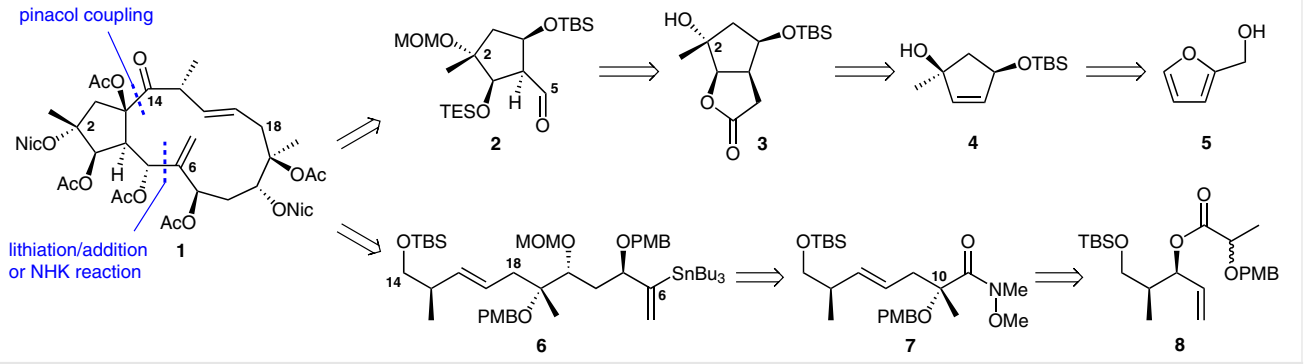
Plants of the genus *Euphorbia* have been common ingredients in herbal folk medicine for thousands of years, and members of this highly diverse plant family have been used for the treatment of a variety of medical conditions.[2] In the last century, phytochemists became interested in active ingredients and numerous biologically active natural products, among them the tiglianes, daphnanes, and the jatrophanes were isolated.[3] Despite their fascinating structural and biological properties only few synthetic studies toward jatrophane diterpenes have been published.[4]

In 2001, the highly oxygenated diterpene euphosalicin (**1**) was isolated from *Euphorbia salicifolia* by Hohmann and co-workers.[5] Although it has a unique [11.3.0] bicyclic structure, it is closely related to the jatrophanes: formal incorporation of the jatrophane C18 methyl group into the macrocycle gives the euphosalicin skeleton as shown in Figure 1.

From a biological point of view, **1** is a potent inhibitor of P-glycoprotein,[6] an adenosine triphosphate-dependent transporter responsible for the efflux of druglike molecules from cells.[7] Many types of cancer lines overexpress this transporter, leading to multidrug resistance, which is a major reason for cancer chemotherapy to fail.[8] Thus, blocking P-glycoprotein is a promising approach to increasing the efficacy of existing anticancer drugs.

The intriguing structure – the dense functionalization and uncommon framework – in combination with the promising biological properties prompted us to search for a synthetic route toward euphosalicin (**1**). A few years ago, we reported a concise route to the cyclopentane fragment of the title compound.[4k,l] Herein, we describe the preparation of the requisite C6–C14 fragment of euphosalicin.

The retrosynthetic analysis is outlined in Scheme 1. We intended to employ a derivative of a previously prepared cyclopentane fragment, namely five-membered-ring synthon **2**[4k,l] which should be connected to the C6–C14 fragment **6** of euphosalicin (**1**) under lithiation conditions or by means of a Nozaki–Hiyama–Kishi (NHK) reaction. The 13-membered macrocycle should then be elaborated using a pinacol coupling reaction. The key intermediate in the preparation of fragment **6** was Weinreb amide **7**, which we envisaged to construct through an Ireland–Claisen rearrangement[9] of **8**. This would ensure the *E* configuration of the internal alkene, allow us to easily set the quaternary C10 stereocenter, as well as derive both stereogenic centers



Scheme 1 Retrosynthetic analysis of euphosalicin

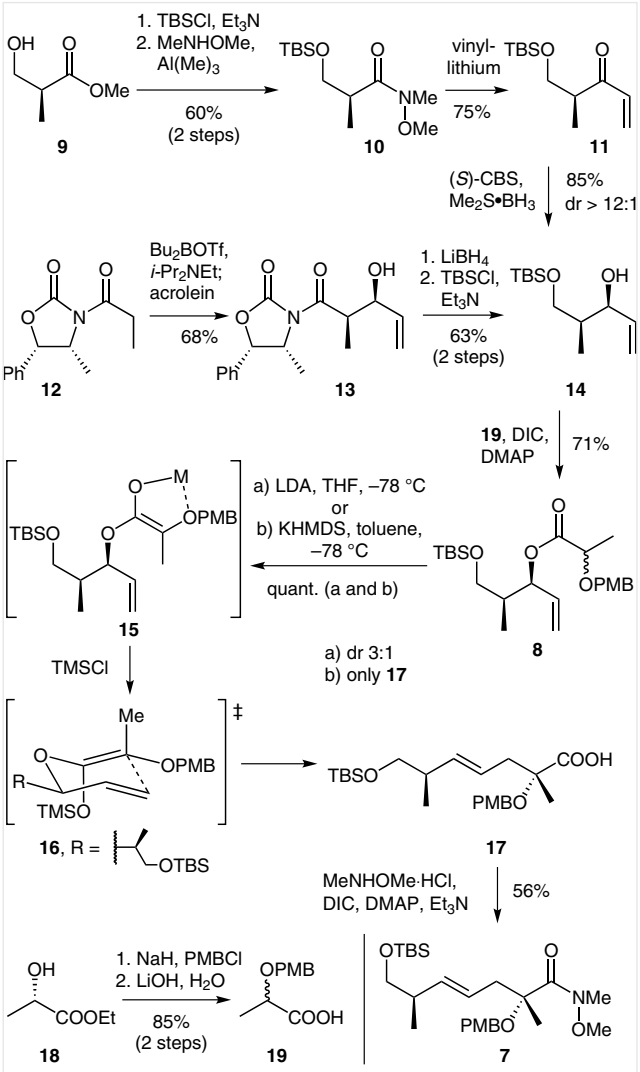
in **7** from the same source of chirality. Compound **8** should be accessible through Evans aldol chemistry or from Roche ester **9** via a short synthetic sequence.

The synthesis of the C6–C14 fragment of euphosalicin started with the preparation of monoprotected diol **14**, as outlined in Scheme 2. Silylation of (*R*)-Roche ester (**9**) and subsequent exposure to *N*,*O*-dimethylhydroxylamine and trimethyl aluminum furnished Weinreb amide **10**, which was reacted with vinyl lithium. The newly formed vinyl ketone **11** was then reduced in the presence of the chiral Corey–Bakshi–Shibata (CBS) oxazaborolidine and monoprotected diol **14** was obtained in excellent yield and good diastereoselectivity (dr >12:1).

An alternative route toward **14** proceeded via an Evans aldol reaction[10] of **12** to give **13**, followed by reductive removal of the auxiliary. Selective mono-TBS protection and esterification[11] of the remaining free hydroxyl group with PMB-protected lactic acid **19**[12] yielded building block **8**.

With two reliable routes to monosilylated diol **8** at hand, we proceeded to develop conditions for the crucial [3,3]-sigmatropic rearrangement. The controlled generation of the C10 stereocenter in the envisaged Ireland–Claisen reaction relied on the selective formation of the desired enolate geometry as well as on the rearrangement transition-state geometry favoring the desired product. In the rearrangement of **8**, the first prerequisite should be satisfied by the α-oxygenation on the ester, which Kallmerten showed to strongly favor (*Z*)-silyl enol ethers, presumably due to chelation effects (**15**).[13] The second requirement should be ensured by the preferentially equatorial positioning of the R group in the rearrangement transition state **16**.

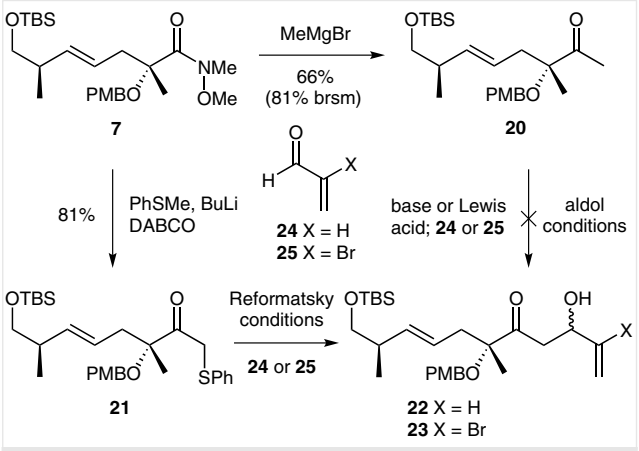
When **8** was subjected to LDA followed by TMSCl at –78 °C and left to warm to room temperature, clean rearrangement to **17** was observed. However, analysis of the resulting material revealed a diastereomeric ratio of only 3:1. Separation of this mixture by HPLC was not possible, likely because of the marginal interaction between the remote stereocenters. Acid **17** was reacted with a number of chiral alcohols, but the resulting esters did not allow the separation of the diastereomers either. Other reaction conditions



Scheme 2 Preparation of Weinreb amide **7**

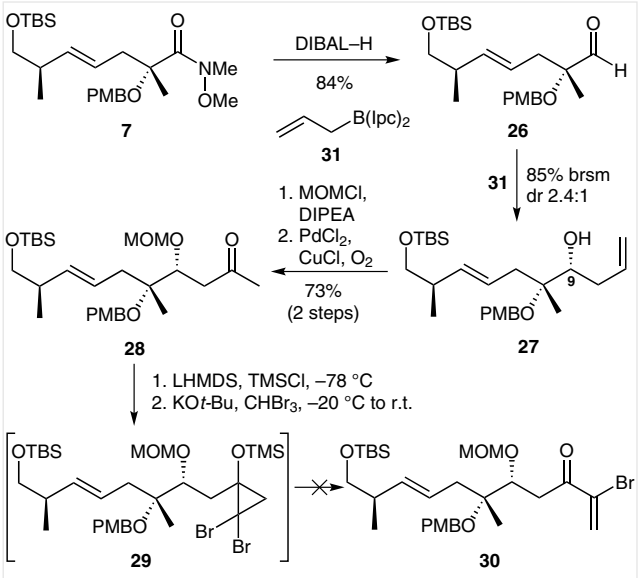
were screened with the hope of increasing the diastereomeric ratio to a synthetically viable point. Different solvents, enolization temperatures, or lithium bases did not give significantly better results. Inspired by a 1999 report from Langlois,[14] we investigated the use of KHMDS as base. Fortunately, desired acid **17** was obtained as single isomer when **8** was treated with KHMDS followed by TMSCl and warmed to –20 °C.[15] Without further purification, Weinreb amide **7** was obtained upon exposure of acid **17** to *N*,*O*-dimethylhydroxylamine hydrochloride, *N*,*N*′-diisopropylcarbodiimide (DIC) and base.

Our initial strategy toward the C6–C14 fragment of euphosalicin envisaged the formation of methyl ketone **20** from Weinreb amide **7** (Scheme 3) and the utilization of this compound in aldol reactions with either acrolein (**24**) or bromoacrolein (**25**). Thus, **7** was reacted with methyl magnesium bromide which delivered methyl ketone **20** in good yield. However, despite numerous attempts, aldol reactions of **20** with **24** or **25** failed to give the desired products. Under basic conditions, complete deprotonation of the methyl ketone was proven by D_2O quench, but the generated enolate did not add to aldehydes even at elevated temperatures. Lewis acidic conditions led to rapid decomposition. We reasoned that Reformatsky conditions might be better suited to access the desired fragment, and thioether **21** was prepared via addition of $PhSCH_2Li$ to Weinreb amide **7**.[16] Unfortunately, all attempts to generate **22** or **23** from thioether **21** were also met with failure.



Scheme 3 Aldol approach toward fragments **22** or **23**

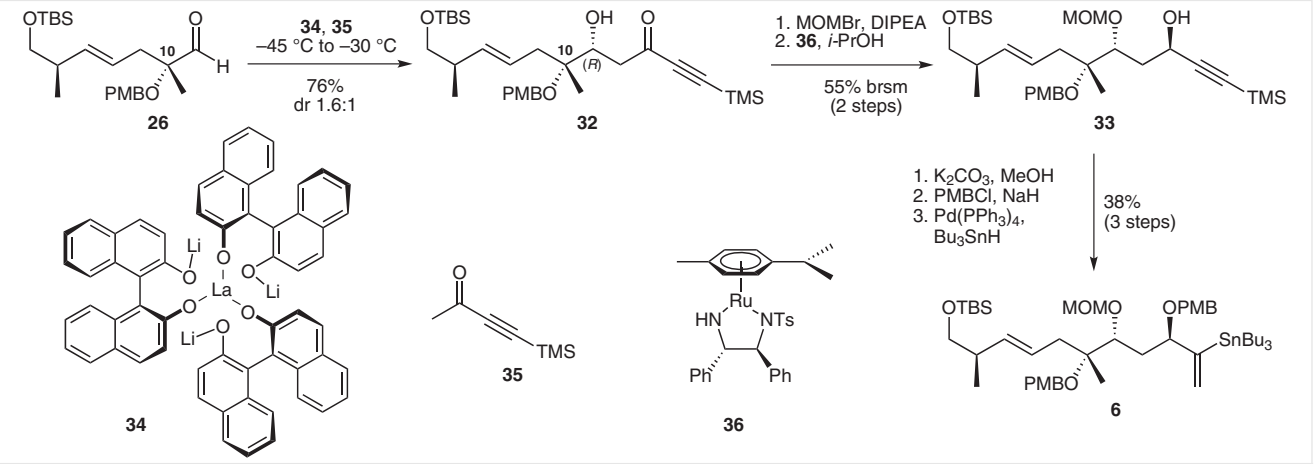
An interesting sequence for the elaboration of α-bromo-α,β-unsaturated ketone motifs was reported by Ohshiro several years ago.[17] The route featured the cyclopropanation of a silyl enol ether. The subsequent rearrangement with loss of one halide and opening of the cyclopropane ring delivered the desired halogenated enone. We wished to evaluate this method and prepared methyl ketone **28** as synthon for this transformation (Scheme 4). The route commenced with DIBAL-H reduction of Weinreb amide **7** which cleanly furnished aldehyde **26**. Brown allylation[18] then delivered homoallyl alcohol **27** in excellent yield but low stereoselectivity. Other allylation protocols, for example utilizing the Duthaler–Hafner catalyst,[19] resulted in improved product ratios, but the yields were generally lower.



Scheme 4 Rearrangement route to bromoenone **30**

The diastereomers could easily be separated by means of flash column chromatography. The stereochemical assignment of the newly installed hydroxyl moiety at C9 in **27** was accomplished by means of detailed NOE studies of the corresponding cyclic PMP acetal, obtained by oxidation of the PMB ether in **27** (cyclic intermediate not shown; for a similar strategy see the oxidation of *epi*-**32**, Scheme 6). Subsequent protection of the desired major product as MOM ether was followed by Wacker oxidation[20] of the terminal double bond. Methyl ketone **28**, the precursor for the key cyclopropanation reaction, was isolated in excellent yield. While enolization and silylation could be cleanly effected, exposure of the resulting alkene to dibromocarbene sources led to the isolation of starting material or to decomposition. As all attempts to isolate bromoenone **30** were met with failure, we started searching for a more predictable route.

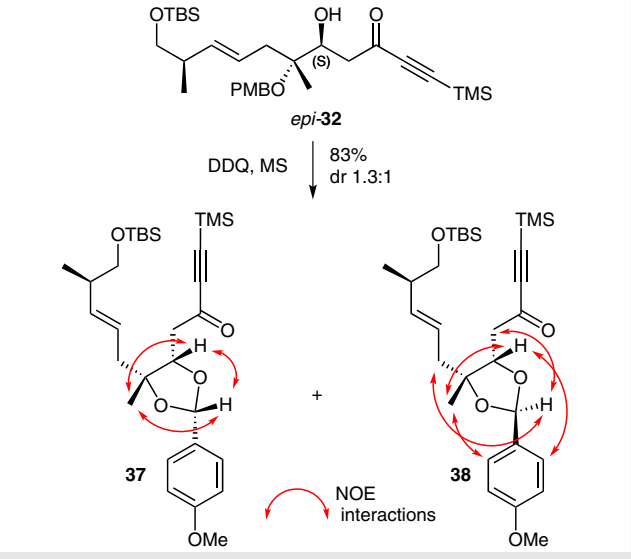
We turned our attention to the aldol reactions of aldehyde **26**. As the reaction of **26** with either methyl vinyl ketone or the corresponding brominated derivative failed to deliver the desired products in acceptable yield (reactions not shown), the approach depicted in Scheme 5 emerged as the most promising route to fragment **6**. Aldehyde **26** was treated with Shibasaki's (*S*)-LLB catalyst[21] (**34**) and butynone **35** to give **32** as a mixture of diastereomers with 76% yield and a diastereomeric ratio of 1.6:1. The quaternary stereocenter at C10 and the presence of an oxygen functionality in α-position of the acceptor in this key Shibasaki direct aldol reaction (**26**) could be responsible for the un-



Scheme 5 Final steps to the C16–C14 fragment of euphosalicin

usually low level of stereoselectivity. We reasoned that the oxygen at C10 might take part in the formation of competing chelated intermediates, resulting in the observed decreased stereoinduction.

Chromatographic purification proved difficult, as **32** readily decomposed on silica. However, the problem could be solved by performing flash chromatography at –25 °C.[22] The relative stereochemistry of the minor isomer *epi*-**32** was determined by oxidation of the PMB ether to the cyclic PMP acetal. A mixture of two cyclic products **37** and **38** was obtained, differing in the stereochemistry of the acetal position. Analysis of NOE correlations (Scheme 6) confirmed the desired stereochemical configuration in the major aldol product **32**.



Scheme 6 NOE correlations in cyclic PMP acetals **37** and **38**

Next, the secondary alcohol in **32** was protected as ether using MOMBr (lower yield was observed when MOMCl was used). Purification was again performed at low temperatures due to stability concerns. The following transfer hydrogenation using Noyori's catalyst[23] (**36**) smoothly produced **33** in good yield without any trace of the undesired epimer.[24] The resulting product was stable on silica gel, allowing for easier purification.

The sequence continued with a K_2CO_3/MeOH-mediated TMS cleavage[25] and PMB protection of the propargylic alcohol. At this stage, we examined several methods of hydrometalating or hydrohalogenating the alkyne. The typically harsh conditions of acidic or radical hydrohalogenations seemed unsuitable for our substrate. Trost's ruthenium-catalyzed hydrosilylation[26] proceeded with great regioselectivity in moderate yields, but we were unable to elaborate the resulting vinyl silane into a viable synthetic handle. In our hands, Hoveyda's nickel-based hydroalumination,[27] while delivering excellent results for several substrates, did not work for alkynes with oxygenation in the propargylic position. Finally, we resorted to transition-metal-catalyzed hydrostannylations. $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$,[28] and $RhCl(CO)(PPh_3)_2$[29] all gave broadly similar results, with $Pd(PPh_3)_4$ generally giving the best yields and selectivities. In all cases we observed reduction of the alkyne to the double bond as side reaction. The desired hydrostannylated material **6** was formed along with minor amounts of reduction product and of a linear product with the tributyltin moiety at the terminal position. The three-component mixture was easily separable on silica gel, allowing the isolation of the desired coupling precursor **6** in acceptable yield.

Summarizing, our route provides access to the desired C6–C14 fragment of euphosalicin in reliable 13 steps and in quantities sufficient for the completion of the synthesis of the natural product. With **6** in hand, future efforts are di-

rected toward the elaboration of suitable coupling protocols with the previously synthesized five-membered-ring synthon **2**.

Acknowledgment

We thank the Austrian Science Fund (FWF) for financial support (FWF-R45-N19 and FWF-P20697-N19).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380422.

References and Notes

(1) Current address: Uwe Rinner, Institute of Organic Chemistry, Johannes Kepler University Linz, Altenberger Straße 69, 4040 Linz, Austria.
(2) (a) Mwine, J. T.; Van Damme, P. *J. Med. Plants Res.* **2011**, *5*, 652. (b) Graham, J. G.; Quinn, M. L.; Fabricant, D. S.; Farnsworth, N. R. *J. Ethnopharmacol.* **2000**, *73*, 347.
(3) (a) Shi, Q. W.; Su, X. H.; Kiyota, H. *Chem. Rev.* **2008**, *108*, 4295. (b) Vasas, A.; Hohmann, J. *Chem. Rev.* **2014**, *114*, 8579.
(4) (a) Rinner, U. *Eur. J. Org. Chem.* **2015**, *15*, 3197. (b) Smith, A. B.; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219. (c) Smith, A. B.; Lupo, A. T.; Ohba, M.; Chen, K. *J. Am. Chem. Soc.* **1989**, *111*, 6648. (d) Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8465. (e) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692. (f) Helmboldt, H.; Rehbein, J.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 289. (g) Helmboldt, H.; Köhler, D.; Hiersemann, M. *Org. Lett.* **2006**, *8*, 1573. (h) Helmboldt, H.; Hiersemann, M. *J. Org. Chem.* **2009**, *74*, 1698. (i) Schnabel, C.; Hiersemann, M. *Org. Lett.* **2009**, *11*, 2555. (j) Yamamura, S.; Shizuri, Y.; Kosemura, S.; Ohtsuka, J.; Tayama, T.; Ohba, S.; Ito, M.; Saito, Y.; Terada, Y. *Phytochemistry* **1989**, *28*, 3421. (k) Gilbert, M.; Galkina, A.; Mulzer, J. *Synlett* **2004**, 2558. (l) Mulzer, J.; Giester, G.; Gilbert, M. *Helv. Chim. Acta* **2005**, *88*, 1560. (m) Shimokawa, K.; Takamura, H.; Uemura, D. *Tetrahedron Lett.* **2007**, *48*, 5623. (n) Lentsch, C.; Rinner, U. *Org. Lett.* **2009**, *11*, 5326. (o) Mohan, P.; Koushik, K.; Fuertes, M. J. *Tetrahedron Lett.* **2012**, *53*, 2730. (p) Mohan, P.; Fuertes, M. J. *Tetrahedron Lett.* **2013**, *54*, 3919. (q) Fürst, R.; Rinner, U. *J. Org. Chem.* **2013**, *78*, 8748. (r) Fürst, R.; Lentsch, C.; Rinner, U. *Eur. J. Org. Chem.* **2013**, 2293. (s) Lentsch, C.; Fürst, R.; Rinner, U. *Synlett* **2013**, *24*, 2665. (t) Lentsch, C.; Fürst, R.; Mulzer, J.; Rinner, U. *Eur. J. Org. Chem.* **2014**, 919. (u) Fürst, R.; Lentsch, C.; Rinner, U. *Synthesis* **2014**, *46*, 357.
(5) Hohmann, J.; Evanics, F.; Dombi, G.; Molnar, J.; Szabo, P. *Tetrahedron* **2001**, *57*, 211.
(6) Vasas, A.; Sulyok, E.; Redei, D.; Forgo, P.; Szabo, P.; Zupko, I.; Berenyi, A.; Molnar, J.; Hohmann, J. *J. Nat. Prod.* **2011**, *74*, 1453.
(7) Goldman, B. *J. Nat. Cancer Inst.* **2003**, *95*, 255.
(8) Eckford, P. D. W.; Sharom, F. J. *Chem. Rev.* **2009**, *109*, 2989.
(9) For a general overview, see: *The Claisen Rearrangement: Methods and Applications*; Hiersemann, M.; Nubbemeyer, U., Eds.; Wiley-VCH: Weinheim, **2007**.
(10) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(11) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(12) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4573.
(13) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177.
(14) Picoul, W.; Urchegui, R.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4797.
(15) Chromatographic separation proved to be impossible. The ratio of stereoisomers was solely determined based on NMR data.
(16) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429.
(17) Hirao, T.; Hayashi, K.; Fujihara, Y.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1985**, *50*, 279.
(18) (a) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065. (b) Sun, H.; Roush, W. R. *Org. Synth.* **2011**, *88*, 87.
(19) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807.
(20) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth.* **1984**, *62*, 9.
(21) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733.
(22) See the Supporting Information for a detailed description of our setup.
(23) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.
(24) The relative stereochemistry was proven via NOE correlation analysis of a cyclic acetonide analogue of 23.
(25) Ohkubo, M.; Hirai, G.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 3862.
(26) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726.
(27) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961.
(28) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(29) (a) Tsang, D. S.; Yang, S.; Alphonse, F.-A.; Yudin, A. K. *Chem. Eur. J.* **2008**, *14*, 886. (b) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881.