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Catalytic Enantioselective Total Syntheses of Bakkenolides I, J, and S: Application of a Carbene-Catalyzed Desymmetrization

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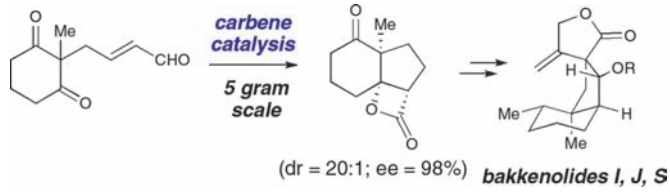
ABSTRACT



A general strategy for the catalytic asymmetric syntheses of the bakkenolides is reported. The key bond-forming step involves an *N*-heterocyclic carbene catalyzed desymmetrization of a 1,3-diketone to form three new bonds in one step with excellent enantio- and diastereoselectivity. This intramolecular reaction allows direct access to the hydrindane core of the bakkenolide family and enables a facile synthesis of these natural products.

The bakkanes are a large class of sesquiterpene natural products containing a characteristic cis-fused 6,5-bicyclic core.[1] The first isolation of a bakkane was reported in 1968, and ensuing investigations have identified over 50 members in this family.[2] The bakkenolides are biogenetically related to the eremophilanes, and the conversion of the initial decalin core to the 6,5 system is proposed to involve an intriguing oxidative ring contraction.[3] These natural products possess a wide spectrum of biological activity including antifeedant effects, platelet aggregation inhibition, and potent inhibitory activity against a variety of tumor cell lines.[4] The five contiguous stereocenters around the hydrindane core, including two quaternary carbons and the spiro γ-butyrolactone, present an inspiring challenge to the application of modern asymmetric methodology.

With their compact topology combined with useful biological activity, this natural product family has elicited considerable attention since the total synthesis of (±)-bakkenolide A by Evans.[5] The majority of syntheses of the bakkenolides are racemic and have relied on efficient Diels−Alder or [2 + 2] cycloadditions to build the hydrindane core.[6] The asymmetric synthetic approaches reported to date rely primarily on chiral pool technology. Recent asymmetric work by Silva begins with the Wieland−Miescher ketone and is highlighted by a novel ring contraction.[7] Two examples reported previously start with carvone[8] or employ (−)-*N*-methylephedrine reduction technology.[6b] The dearth of *catalytic* enantioselective approaches to these molecules

(1) (a) Silva, L. F. *Synthesis* **2001**, 671. (b) Brocksom, T. J.; Brocksom, U.; Constantino, M. G. *Quim. Nova* **2008**, *31*, 937.

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(3) (a) Reference 2. (b) Marshall, J. A.; Cohen, G. M. *J. Am. Chem. Soc.* **1971**, *36*, 877–882.

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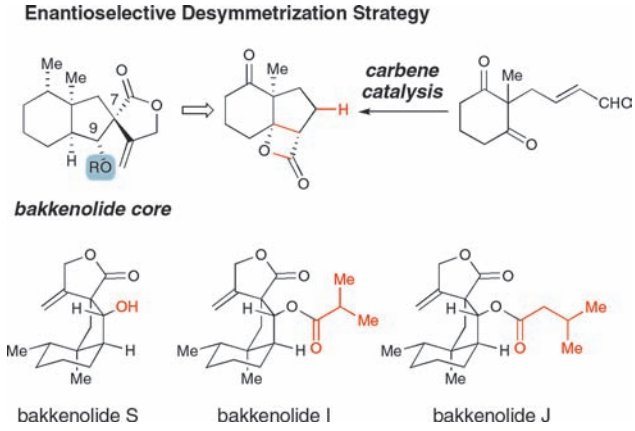
to date is an opportunity to challenge the boundaries of asymmetric catalysis in the context of synthesis and provide new means to efficiently prepare optically active bakkanes.

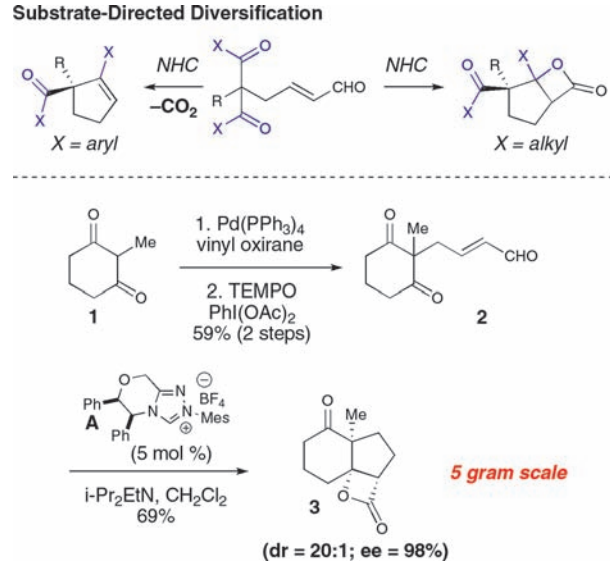
The field of N-heterocyclic carbene catalysis has undergone significant development recently,[9] and its application in complex molecule synthesis is an emerging area.[10] Carbene catalysis provides efficient access to a variety of nucleophilic species (e.g., acyl anion, homoenolate, enolate) with high levels of stereoselectivity and is particularly attractive for integration into synthetic strategies as a key bond-forming tactic. We report herein the efficient, enantioselective total syntheses of (−)-bakkenolides I, J, and S utilizing a cascade homonenolate protonation/intramolecular aldol/acylation sequence catalyzed by an N-heterocyclic carbene (NHC) (Scheme 1).

Scheme 1. Synthetic Approach



The key structural element in this family of natural products is the fused 6,5-bicyclic ring system that contains an angular methyl group flanked by tertiary and spiro quaternary carbon atoms. We envisaged the core of these molecules being synthesized using our recently reported NHC-catalyzed desymmetrization of 1,3-diketones (Scheme 2).[11] This strategy would allow us to control the formation of the key quaternary stereogenic center present in all the

Scheme 2. NHC-Catalyzed Desymmetrization



bakkenolides starting from readily available material and produce appropriate functional groups for further elaboration.

The synthesis of the required symmetric 1,3-diketone began with the palladium-catalyzed addition of 2-methy-1,3-cyclohexadione (**1**) to butadiene monoepoxide. A subsequent TEMPO-catalyzed oxidation of the allylic alcohol furnished the α,β-unsaturated aldehyde (**2**, 59% for two steps). In the key bonding-forming event, the achiral aldehyde (**2**) underwent a tandem homoenolate protonation, intramolecular aldol addition, and acylation in the presence of 5 mol % **A** and generated the desired β-lactone **3** in 69% yield.

An interesting facet of this reaction is the isolation of the β-lactone product. In our 2007 work with this desymmetrizing aldol reaction,[11] substrates with aromatic ketones readily decarboxylate under the reaction conditions to yield substituted cyclopentene rings.[12] This highly selective desymmetrization reaction can be performed on a 5 g scale and affords the tricyclic product with excellent levels of diastero- and enantioselectivity (>20:1 dr, 98% ee). The concentration was increased, and the reaction temperature was lowered from 40 to 35 °C to accommodate larger reaction scales, which slightly improved both the yield and enantioselectivity.

With β-lactone **3** in hand, the installation of an oxygen atom directly to the C-9 position was required. As a prelude

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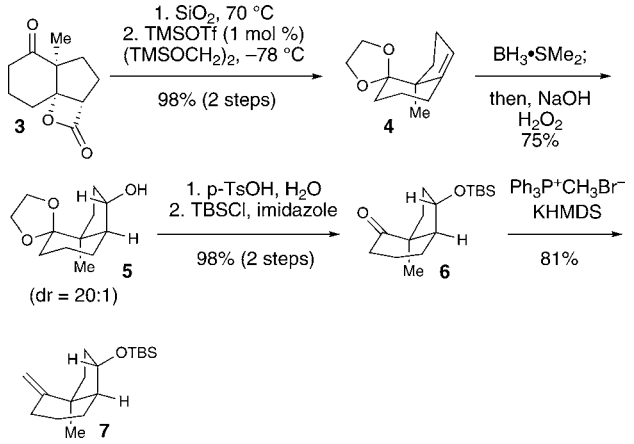
(10) For total syntheses employing carbene catalysis, see: (a) Trost, B. M.; Shuey, C. D.; Dininno, F. *J. Am. Chem. Soc.* **1979**, *101*, 1284–1285. (b) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514. (c) Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713–2716. (d) Koyama, Y.; Yamaguchi, R.; Suzuki, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 1084–1087. (e) Nicolaou, K. C.; Nold, A. L.; Li, H. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5860–5863.

(11) Wadamoto, M.; Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099.

(12) For the first report of this decarboxylation in carbene-catalyzed reactions to yield cyclopentenes (although prurportedly through a homoenolate and not enolate pathway), see: Nair, V.; Vellalath, S.; Poonoth, S.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736–8737.

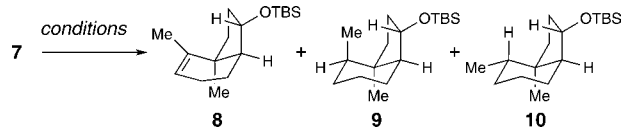
to this oxidation, the decarboxylation of **3** in the presence of silica gel[13] followed by protection of the ketone using Noyori's protocol allowed for the successful installation of the ketal, whereas typical Dean−Stark conditions resulted in poor yields.[14] A hydroboration of the alkene occurred from the convex face of **4**, resulting in formation of the secondary alcohol in a high yield (75%) with >20:1 regio- and diastereoselection. The reformation of the ketone was facilitated with *p*-TsOH in acetone followed by protection of the secondary alcohol with TBSCl and imidazole (98% yield for two steps). A subsequent Wittig olefination of the sterically hindered ketone **6** successfully installed the *exo*-methylene subunit of **7** (81%) (Scheme 3).

Scheme 3. Construction of Olefin **7**



The reduction of the newly formed alkene within **7** to generate the necessary vicinal methyl substituents was not straightforward. A survey of numerous reduction conditions yielded at best a 1:1 ratio of the desired diastereomer **10** and **9**. The use of Et_3SiH in combination with Pd/C and H_2 led to an increase in **10** but also promoted isomerization to the endocyclic olefin (**8**) (Table 1).[15] This observation proved

Table 1. Formation of Olefin **8**



entry	conditions	**8**:**9**:**10**[a]
1	Pd/C, H_2, EtOH	0:1:1
2	PtO_2, H_2, MeOH	0:2:1
3	Pd/C, H_2, PhH, Et_3SiH	1:1:2
4	$PdBaSO_4$, H_2, EtOH	2:1:1
5	Pd/C, H_2, toluene, 110 °C[b]	NR
6	(cod)(pyr)(PCy_3)$IrPF_6$, H_2	1:0:0[c]

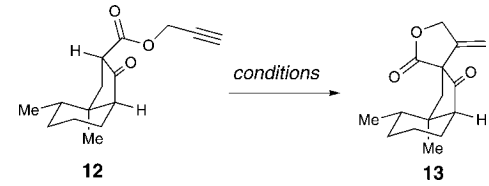
[a] Ratio determined by ^1H NMR spectroscopy; [b] Reaction exposed to H_2 for 5 min and was then sealed; [c] 99% isolated yield.

fortuitous since alkene **8** could be independently converted to **10** and **9** in a 6:1 ratio in the presence of Pd/C and hydrogen at elevated pressure. With these results in hand, we explored conditions to promote the isomerization cleanly since this reaction followed by the stereoselective reduction would be the superior route (**7** to **8** to **10**). Exposure to mild reduction conditions such as $PdBaSO_4$ in the presence of H_2 improved the ratio, but the results were not satisfactory. Attempts at isomerization with elevated reaction temperatures also failed to improve the efficiency of the reaction. Finally, we found that 1 mol % of Crabtree's catalyst ([(cod)(pyr)(PCy_3)Ir]PF_6)[16] successfully provided internal alkene **8** in 99% yield from **7**, which allowed us to proceed with the Pd/C reduction to afford **10** (69%). Minimized structures of **8**, **9**, and **10** (MM2 Spartan) suggest that there are subtle torsional effects that control the facial selectivity of this reduction. The undesired isomer **9** is higher in energy than **10** due to the axial methyl group, and this difference may direct a more late-type transition state for this hydrogenation.

The conversion of silyl ether **10** to ketone **11** was accomplished with TBAF followed by Dess−Martin periodinane (98%, two steps). An acylation of the kinetic enolate with Mander's reagent[17] followed by trans-esterification with propargyl alcohol yielded *β*-keto propargyl ester **12** as a 9:1 mixture of diastereomers.[18]

At this juncture, the formation of the key butyrolactone using a Conia−ene reaction was investigated (Table 2).[19]

Table 2. Investigation of Lactone Formation



entry	conditions	yield[a] (%)	dr[b] (%)
1	5 mol % (PPh_3)AuCl, AgOTf, CH_2Cl_2	<5	
2	5 mol % [(PPh_3)Au)$_3$O]BF_4, HOTf, DCE	<5	
3	$Mn(OAc)_3 \cdot H_2O$, EtOH	70	20:1

[a] Isolated yield. [b] As determined by ^1H NMR spectroscopy.

While this method was quite effective with *β*-ketoesters with the alkyne previously installed on the α-carbon, to our

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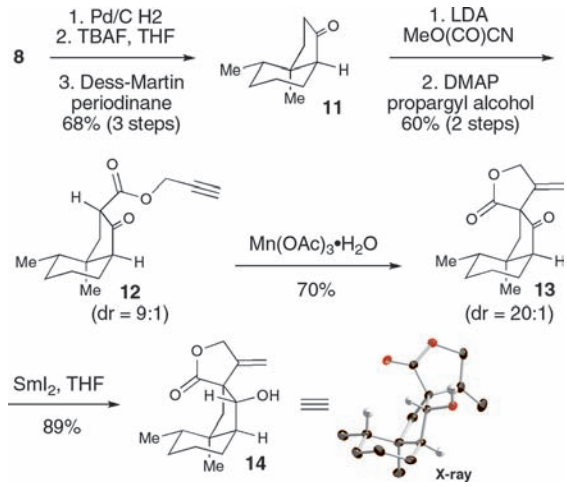
knowledge there are no reports of the cyclization occurring from the propargyl ester. Unfortunately, this route led to only minor amounts of product.

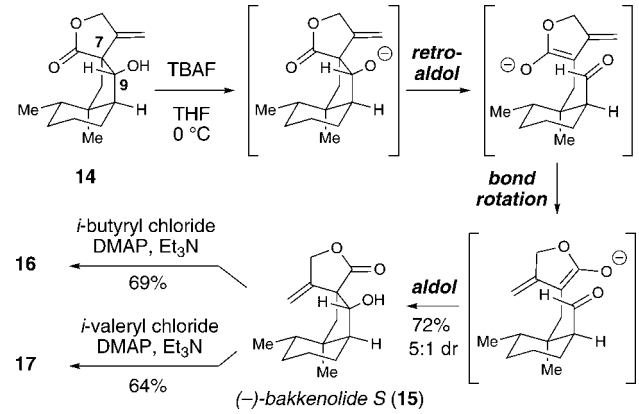
After this approach proved unsuccessful, we resorted to the ring-closure protocol and final synthetic sequence initially developed by Greene and Deprés.[6d] The exposure of **12** to $Mn(OAc)_3$ promoted a highly diastereoselective cyclization, thereby providing the spirocyclic lactone in good yield (70%) as a single diastereomer.[20,21] A chemoselective reduction of the ketone using SmI_2 provided β-hydroxy ester **14** in 89% yield and 20:1 dr (Scheme 4). The relative stereochemistry of **14** was confirmed by X-ray analysis.[22]

Scheme 4. Construction of Alcohol **14**



The construction of the spiro lactone was high yielding and selective, but produced the undesired epimer at the C7 position. Fortunately, the β-hydroxy lactone skeleton of **14** allows for a possible retro-aldol/aldol process to access the desired diastereomer. Following the elegant prior reports on the bakkenolides using this strategy by Deprés,[23,6d] the treatment of **14** with TBAF promotes a C7−C9 scission followed by an intramolecular aldol reaction between the intermediate lactone enolate and transient aldehyde to afford a 5:1 mixture of (−)-bakkenolide S (**15**) and **14** (72%).[24] This thermodynamically driven process favors **15** presumably due to the placement of the hydroxyl group on the convex face and then hydrogen bonding between this alcohol and the lactone carbonyl oxygen. Due to the challenges separating the bakkenolide S/**14** mixture by standard chromatography, the transformation of alcohol **14** to (−)-bakkenolides I (**16**) and J (**17**) via bakkenolide S was accomplished by direct addition of either isobutyryl chloride (69%) or isovaleryl chloride (64%) to the unpurified TBAF reaction (Scheme 5).

Scheme 5. Synthesis of Bakkenolides I, J, and S



In summary, a catalytic enantioselective strategy for the syntheses of the bakkenolide core has been established. These studies demonstrate the utility of the intramolecular carbene-catalyzed desymmetrization reaction which provides the bakkane scaffold by forming three new bonds in a single step in 98% ee and >20:1 dr from a simple achiral precursor. The elaboration of the hydrindane architecture through Deprés and Greene's lactone closure and retro-adol sequence furnishes the natural enantiomers of bakkenolide I, J, and S. Since the successful carbene-catalysis strategy does not rely on starting from chiral pool materials, it provides the impetus for us to explore these compounds and related structural analogs in biological and medical settings. Our continued studies using carbene catalysis in total synthesis to construct target molecules with stereochemical control and expediency will be reported in due course.

Acknowledgment. Support for this work was provided by NIGMS (RO1GM73072), Amgen, the Sloan Foundation, GlaxoSmithKline, and AstraZeneca. E.M.P. is a recipient of a 2008−2009 ACS Division of Organic Chemistry fellowship. We thank Drs. Steve Wittenberger and Thad Franczyk for insightful discussions.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) See ref 6 for the use of $Mn(OAc)_3$ ring closures in the synthesis of the bakkenolides. For a review on Mn(III)-based reactions, see: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339–363.

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(22) See the Supporting Information.

(23) Hamelin, O.; Wang, Y.; Deprés, J. P.; Greene, A. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 4314–4316.

(24) The synthesis of bakkenolide S using this sequence was reported by Deprés and Greene (see ref 6g) but without any characterization data of the final product.