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Preparation of Alkylidene Indane and Related Scaffolds and Their Further Elaboration to Novel Chemotypes

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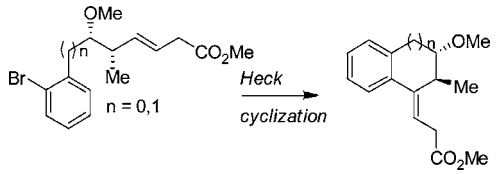
ABSTRACT



Alkylidene indane and ring-expanded scaffolds have been prepared using an enantioselective crotylation/Heck cyclization sequence. Further diversification using consecutive cyclopropanation–Cope rearrangement affords novel chemotypes including spiroindane frameworks.

Diversity-oriented synthesis (DOS) has emerged as a powerful approach to obtain complex molecules for biological studies.[1] The utility of DOS relies ultimately on the development of chemical methodologies for the synthesis of novel structural types with high levels of skeletal and stereochemical complexity.[2] Polyketide natural products possess a broad spectrum of biological activity and both stereochemical and skeletal diversity and have served as an inspiration for complex chemical library design.[3] For instance, our laboratory reported the use of "tagged" organosilanes for enantioselective synthesis of linear polypropionate arrays.[4,5] We anticipated that this methodology could be extended to prepare constrained scaffolds via Heck cyclization of the

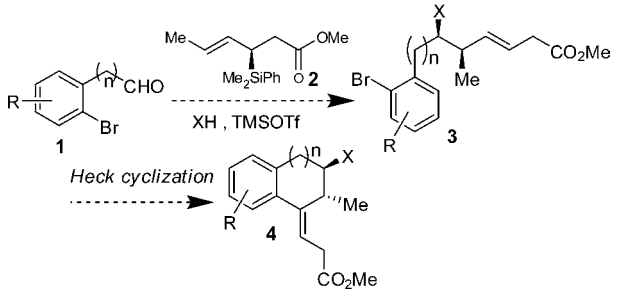


Figure 1. Sequential asymmetric crotylation−Heck cyclization to access alkylidene indane and related scaffolds.

crotylation products (Figure 1). Herein, we report our initial studies to prepare alkylidene indane and related scaffolds

(1) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46. (c) Spring, D. R. *Chem. Soc. Rev.* **2005**, *34*, 472. (d) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74. (e) Arya, P.; Joseph, R.; Gan, Z.; Rakic, B. *Chem. Biol.* **2005**, *12*, 163.

(2) (a) Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004**, *6*, 3009. (b) Gan, Z.; Reddy, P. T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366. (c) Beeler, A. B.; Acquilano, D. E.; Su, Q.; Yan, F.; Roth, B. L.; Panek, J. S.; Porco, J. A., Jr. *J. Comb. Chem.* **2005**, *7*, 673. (d) Adriaenssens, L. V.; Austin, C. A.; Gibson, M.; Smith, D.; Hartley, R. C. *Eur. J. Org. Chem.* **2006**, *22*, 4998. (e) Dandapani, S.; Lan, P.; Beeler, A. B.; Beischel, S.; Abbas, A.; Roth, B. L.; Porco, J. A., Jr.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 8934. (f) Fitzmaurice, R. J.; Etheridge, Z. C.; Jumel, E.; Woolfson, D. N.; Caddick, S. *Chem. Commun.* **2006**, *46*, 4814. (g) Freifeld, L.; Holtz, E.; Dahmann, G.; Langer, P. *Eur. J. Org. Chem.* **2006**, *14*, 3251. (h) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413. (i) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020.

(3) Shang, S.; Tan, D. S. *Curr. Opin. Chem. Biol.* **2005**, *9*, 248.

(4) Kesavan, S.; Su, Q.; Shao, J.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4435.

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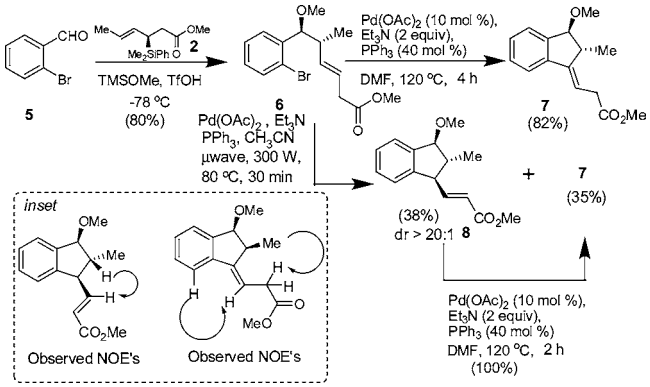
and their further diversification to novel structural motifs including spiroindane frameworks.

Our study began with enantioselective crotylation[6] of 2-bromobenzaldehyde **5** using silane (*R*)-**2** to afford the *syn*-homoallylic ether **6** (dr >20:1, Scheme 1). Heck cyclization[7]

Scheme 1. Preparation of Alkylidene Indane Scaffolds

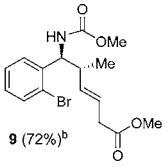
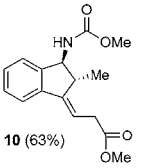
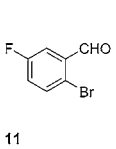
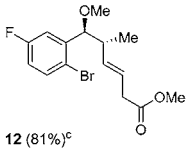
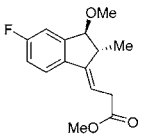
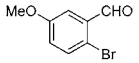
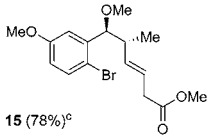
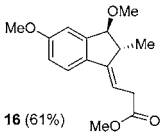
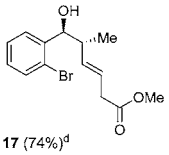
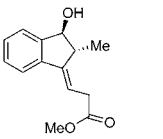
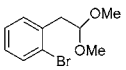
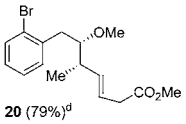
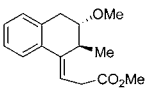
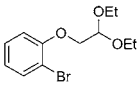
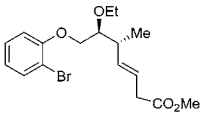
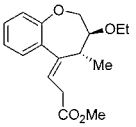


of **6** (cat. $Pd(OAc)_2$, Et_3N, 120 °C) cleanly afforded alkylidene indane **7** (82%).[8] The olefin geometry of **7** was assigned through NOE analysis (inset). Alternatively, performing the Heck cyclization at a lower temperature (80 °C) afforded **7** and trisubstituted indane **8** in 35 and 38% yields, respectively. NOE measurements (inset) indicated that the benzylic vinyl group of **8** was established *trans* to the adjacent methyl group. Subjection of the presumed kinetic product **8** to the Heck reaction conditions ($Pd(OAc)_2$, Et_3N, 120 °C) led to complete isomerization to thermodynamic product **7** where the olefin is conjugated with the aromatic ring.

Table 1 illustrates six bicyclic scaffolds prepared using the diastereo- and enantioselective crotylation−Heck reaction sequence. Various scaffolds bearing both electron-rich and -poor aryl rings (Table 1, entries 2 and 3) and scaffolds with functional handles for further diversification including hydroxyl and carbamate groups (Table 1, entries 1 and 4) were prepared using the two-step sequence. Crotylation of acetal **19**[9] yielded homoallylic ether **20** which was subjected to Heck cyclization to afford tetrahydronaphthalene (**21**). Finally, diethyl acetal **22**[8] was efficiently converted to crotylation product **23** en route to the alkylidene oxepine derivative (**24**).[10]

With access to a number of alkylidene indane and related scaffolds, we turned our attention toward their functional-

Table 1. Additional Bicyclic Scaffolds

entry	substrate	crotylation product (yield)[a]	Heck product (yield)[a,e]
1	 **5**	 **9** (72%)[b]	 **10** (63%)
2	 **11**	 **12** (81%)[c]	 **13** (77%)
3	 **14**	 **15** (78%)[c]	 **16** (61%)
4	 **5**	 **17** (74%)[d]	 **18** (68%)
5	 **19**	 **20** (79%)[d]	 **21** (67%)
6	 **22**	 **23** (71%)[d]	 **24** (48%)

[a] Isolated yield. [b] Reaction conditions: $MeCO_2NH_2$ (1.1 equiv), $BF_3{\cdot}Et_2O$ (1.0 equiv), **2** (1.1 equiv), CH_2Cl_2, −78 to −30 °C. [c] TMSOTf (1.0 equiv), TMSOMe (1.1 equiv), **2** (1.1 equiv), CH_2Cl_2, −78 to −30 °C. [d] TMSOTf (1.0 equiv), **2** (1.1 equiv), CH_2Cl_2, −78 to 30 °C. [e] $Pd(OAc)_2$ (10 mol %), Et_3N (2 equiv), PPh_3 (40 mol %), DMF, 120 °C, 2 h.

ization chemistry. As part of our studies, we considered diazotization of the β,γ-unsaturated ester moiety to a vinyl diazoester. The rich chemistry of diazo compounds provides access to numerous C−C bond forming reactions to generate a variety of functionalized scaffolds[11] and renders them reactive intermediates suitable for DOS.[12] In the event, diazotization of **13** with sulfonyl azide **26**[13] and DBU led to clean formation of the stable vinyl diazoester **27** (Scheme 2). In order to evaluate intermolecular cyclopropanation, **27** was treated with cyclopentadiene in the presence of Rh_2-

(5) (a) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082. (c) Smith, A. B., III; Walsh, S. P.; Frohn, M.; Duffey, M. O. *Org. Lett.* **2005**, *7*, 139. (d) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. L. *Org. Lett.* **2007**, *9*, 1895.

(6) (a) Panek, J. S.; Xu, F. *J. Am. Chem. Soc.* **1995**, *117*, 10587. (b) Jain, N. F.; Cirillo, P. F.; Pelletier, R.; Panek, J. S. *Tetrahedron Lett.* **1995**, *36*, 8727. (c) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475. (d) Beresis, R. T.; Solomon, J. S.; Yang, M. G.; Jain, N. F.; Panek, J. S. *Org. Synth.* **1997**, *75*, 78.

(7) Link, J. T. *Org. React.* **2002**, *60*, 157.

(8) See Supporting Information for complete experimental details.

(9) Garcia-Ruano, J. L.; Aleman, J.; Aranda, M. T.; Fernandez-Ibanez, M. A.; Rodriguez-Fernandez, M. M.; Maestro, M. C. *Tetrahedron* **2004**, *60*, 10067.

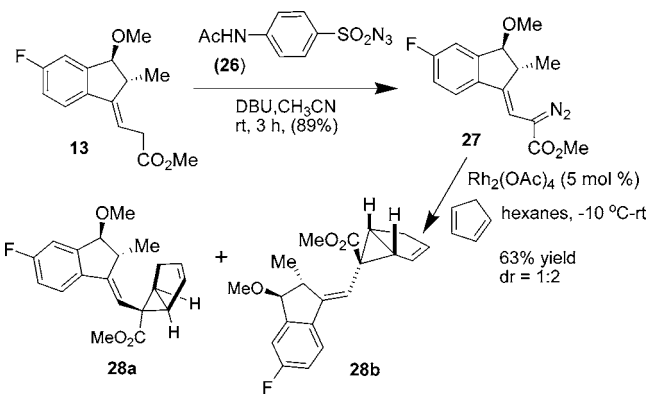
(10) Martins, A.; Marquardt, U.; Kasrvi, N.; Alrerico, D.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 4937.

(11) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 112−162. (b) Mass, G. *Topics in Current Chemistry*; Springer-Verlag: New York; 1987; Vol. 137, pp 75−254.

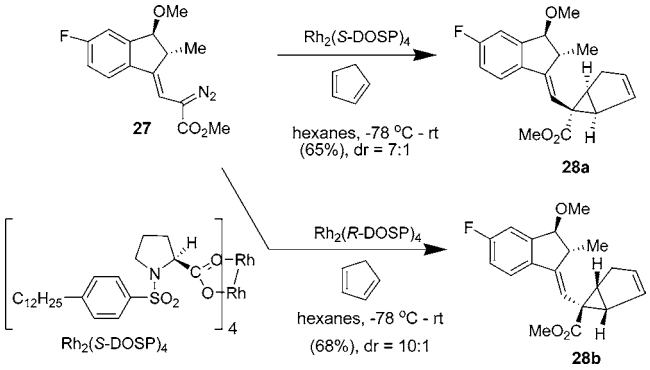
(12) For application of diazo compounds in DOS, see: (a) Oguri, H.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 47. (b) Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. T.; Jessiman, A. S.; Welch, M.; Spring, D. R. *Chem. Commun.* **2006**, 3296. (c) Ni, A.; France, J. E.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5594.

(13) Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.

Scheme 2. Synthesis and Cyclopropanation of a Complex Vinyl Diazoester



Scheme 3. Diastereoselective Cyclopropanations



(OAc)$_4$ (5 mol %) which afforded a mixture of complex divinylcyclopropane products **28a** and **28b** (**28a**/**28b** = 1:2) in 63% yield (Scheme 2). The stereochemistries of both **28a**/**28b** were assigned using NOE measurements as depicted in Figure 2.[8] For both diastereoisomers, the cyclopentene and

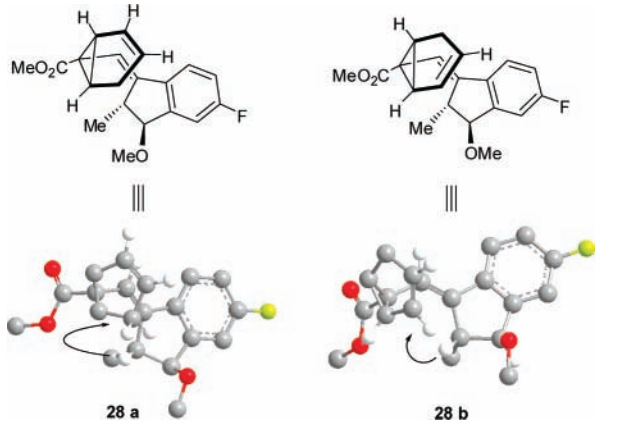


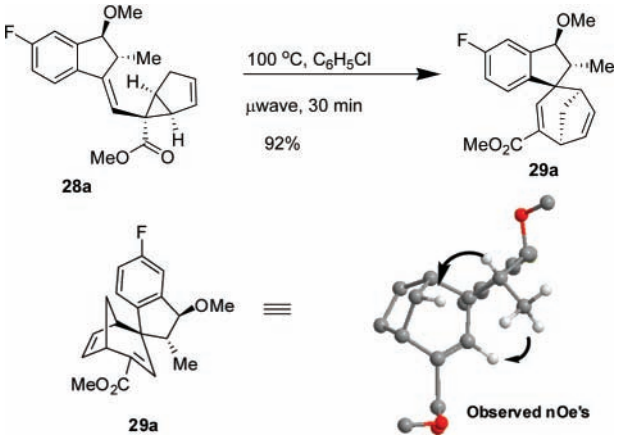
Figure 2. Ground state conformations for divinylcyclopropanes obtained using MOE calculations and their corresponding NOE correlations.

indene units are *cis* to each other[14] and the cyclopropane formed on the face opposite to the allylic methyl group. Conformational search calculations[15] (cf. Figure 2) support the NOE measurements[8] and indicate that, in the major diastereoisomer (**28b**), the newly formed divinylcyclopropane unit is situated in a twist boat-like conformation, while it is forced into a boat-like conformation in the minor diastereoisomer (**28a**) (Scheme 3).

In light of the poor diastereoselection observed in cyclopropanation experiments, we next evaluated use of the chiral dirhodium(II) dicarboxylate catalysts developed by Davies and co workers.[16] Treatment of **27** with cyclopentadiene and the chiral catalyst Rh$_2$(*S*-DOSP)$_4$ (2 mol %) led to isolation of cyclopropane **28a** (65%, dr = 7:1). To our delight, use of the corresponding enantiomeric catalyst Rh$_2$(*R*-DOSP)$_4$ led to isolation of cyclopropane **28b** in excellent diastereoselectivity (dr > 10:1), indicating good catalyst control in a double stereodifferentiating cyclopropanation reaction.

Given our ability to access divinylcyclopropane products, we were positioned to evaluate use of the Cope rearrangement to access spiroindane frameworks (Scheme 4).[17] Previ-

Scheme 4. Cope Rearrangement to a Spiroindane Framework



ous studies by Davies and others have demonstrated the facile Cope rearrangement of *cis*-divinylcyclopropanes to yield seven-membered carbocycles.[13] However, for the present cases, steric interactions in cyclopropanes **28a** and **28b** prevent the Cope rearrangement and allow isolation of the

(14) Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930.

(15) Conformational analysis was conducted using the Molecular Operating Environment (MOE) (version 2006.08) stochastic search.

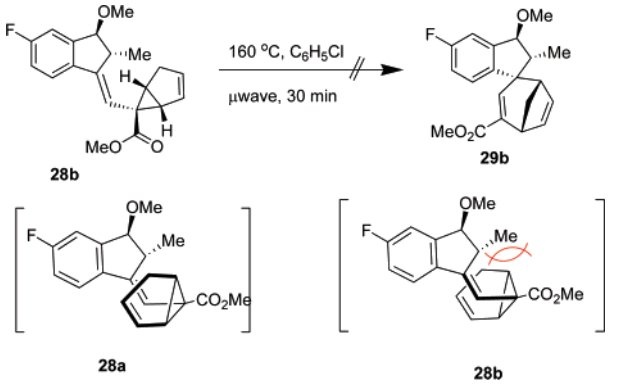
(16) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.

(17) For general reviews on the Cope rearrangement of divinylcyclopropanes, see: (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (b) Hudlicky, T.; Fan, R.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1. (c) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M. ,Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 971.

cyclopropanes at ambient temperature.[18] However, microwave heating of compound **28a** (100 °C, 200 W) led to an efficient divinylcyclopropane rearrangement to yield spiroindane **29a** (92%). The stereochemistry of spiroindane **29a** was assigned using NOE experiments.[8]

Interestingly, subjection of **28b** to the same microwave heating conditions did not lead to the desired divinylcyclopropane rearrangement (Scheme 5) as only starting materials

Scheme 5. Steric Inhibition of the Cope Rearrangement



and decomposition products were recovered. The difference in reactivity of the two diastereoisomers may be explained by destabilizing steric interactions present in the requisite boat-like transition states. In compound **28a**, the cyclopentene unit approaches on the face opposite to the methyl group leading to the formation of product **29a**. On the other hand, when compound **28b** is subjected to thermal rearrangement, the inherent stereochemistry forces the cyclopentene unit to approach on the same face as the methyl group. This unfavorable steric interaction likely inhibits the transformation; use of forcing conditions (up to 160 °C) led to decomposition of starting material likely due to rupture of the cyclopropane ring. A collection of four additional scaffolds derived from the appropriate vinyl diazoesters employing the cyclopropanation rearrangement protocol is shown in Figure 3.

In conclusion, alkylidene indane scaffolds and their ring-expanded variants have been prepared using an enantioselective crotylation−intramolecular Heck reaction sequence. Scaffolds have been further transformed to novel chemotypes, including spiroindanes, utilizing cyclopropanation of derived vinyl diazoesters and microwave-mediated Cope rearrangement. The use of Davies' chiral dirhodium(II) dicarboxylate catalysts allows access to divinylcyclopropane products with high levels of diastereoselection. Application of the methodology described herein to library synthesis and evaluation of the novel chemotypes described in biological assays is currently in progress and will be reported in due course.

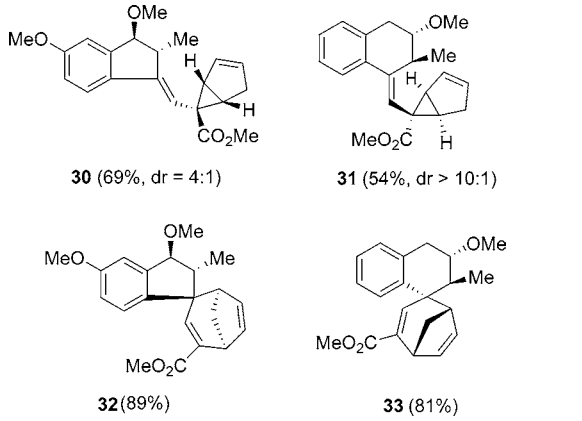


Figure 3. Additional divinylcyclopropane and spirocyclic scaffolds.

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

OL7023778

(18) Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038.