Synthetic Methods

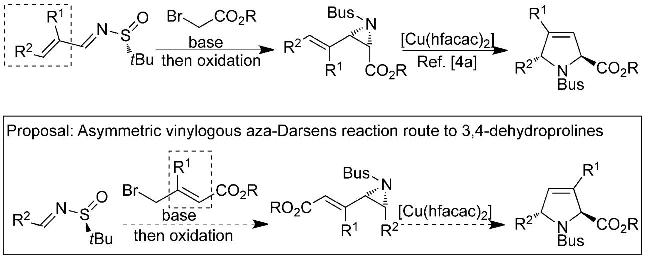
International Edition: DOI: 10.1002/anie.201506559
German Edition: DOI: 10.1002/ange.201506559

Asymmetric [3+2] Annulation Approach to 3-Pyrrolines: Concise Total Syntheses of (−)-Supinidine, (−)-Isoretronecanol, and (+)-Elacomine

*Isaac Chogii and Jon T. Njardarson**

Abstract: *An asymmetric [3+2] annulation reaction to form 3-pyrroline products is reported. Upon treatment with lithium diisopropylamide, readily available ethyl 4-bromocrotonate is deprotonated and trapped with Ellman imines selectively at the α-position to yield enantiopure 3-pyrroline products. This new method is compatible with aryl, alkyl, and vinyl imines. The efficacy of the method is showcased by short asymmetric total syntheses of (−)-supinidine, (−)-isoretronecanol, and (+)-elacomine. This novel annulation approach also works for an aldehyde, thus providing access to a 2,5-dihydrofuran product in a single step from simple precursors. By modifying the structure of the carbanion nucleophile, an asymmetric vinylogous aza-Darzens reaction can be realized.*

The Darzens reaction, wherein the carbanion of an α-halo ester adds to an aldehyde or a ketone to afford an α,β-epoxy ester, is among the oldest named reactions in organic chemistry.[1] By replacing the carbonyl electrophile with an imine, the corresponding aziridine carboxylate esters can be synthesized (aza-Darzens reaction).[2] We recently utilized an asymmetric variant[3] of the aza-Darzens reaction to access vinyl aziridine products, which we used for our copper-catalyzed ring-expansion program (Scheme 1).[4] Inspired by the successful marriage between these two methods to access enantiopure 3,4-dehydroproline products, we postulated that we could access different proline products by using an asymmetric vinylogous aza-Darzens approach in conjugation with our ring-expansion reaction. However, we were surprised by the absence of asymmetric vinylogous aza-Darzens reaction examples, and general lack of investigations toward it. Thus, we focused our initial studies on identifying optimal reaction partners and conditions to access enantiopure aziridines of interest to us, and then upon exposure to our ring-expansion reaction would yield different proline products.[5]



Scheme 1. Proposed asymmetric vinylogous aza-Darzens reaction. Bus = SO_2tBu.

For our initial explorations we employed the readily available ethyl 4-bromocrotonate (**1**) and Ellman imine **2** (Table 1). Treatment of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C and subsequent addition of **2** did not afford any of the expected aziridine product (**4**), but instead the [3+2] annulation (3-pyrroline)[6] product **8** was formed in 22 % yield as a single diastereomer (entry 1). Presumably, the enolate[7] resulting from deprotonation of **1** selectively adds to **2** from its α-position to form **5**, which then undergoes a second deprotonation to the form dienolate **6**. After protonation of **6**, the enoate **7** is most likely formed as an *E/Z* mixture wherein the *Z* enoate undergoes a rapid *5-exo*-tet cyclization to form the 3-pyrroline product **8**. A racemic version of this cascade has previously been observed by Steel and co-workers.[8]

The discovery of this reaction prompted us to optimize the reaction conditions towards maximizing the formation of annulation product **8**. Our efforts first turned to identifying the most suitable base, which proved to be LDA (Table 1, entries 6–12) compared with other bases (entries 3–5). The amount of LDA used is critical for achieving high yields, with three equivalents being ideal. Maintaining low temperatures and using THF as a solvent proved beneficial (entries 7 and 8 versus 6). To suppress the imine self-condensation pathway of alkyl imines,[9] it is important to add the imine slowly as the last component (entries 9–12 versus entry 6).

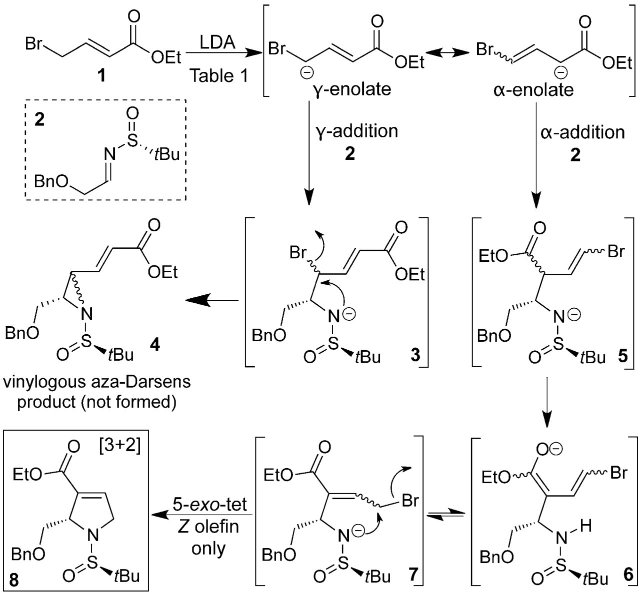
The substrate scope for this new asymmetric [3+2] annulation reaction is demonstrated with the seventeen examples shown in Table 2. All the imines were prepared using Ellman's standard protocol.[10] This new method is broad in scope, thus showing compatibility with aryl, vinyl, and enolizable alkyl imines. Yields for products range from good to very good and diastereoselectivity is uniformly excellent. X-ray crystallography of one of the substrates (**9g**) enabled unambiguous assignment of relative and absolute stereochemistry for the asymmetric annulation reaction. The initial imine addition step proceeds by either an open or closed transition state, however very rapid isomerization of the double bond into conjugation prevents determination of accurate *syn/anti* ratios. Fortunately, this selectivity, or lack thereof, is inconsequential to the success of the reaction as addition to the Ellman imine is completely selective, and the

---

[*] I. Chogii, Prof. Dr. J. T. Njardarson
Department of Chemistry and Biochemistry, University of Arizona
1306 E. University Blvd., Tucson AZ 85721 (USA)
E-mail: njardars@email.arizona.edu
Homepage: http://www.cbc.arizona.edu/njardarson/group

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201506559.

Table 1: Optimizations for a new asymmetric [3+2] annulation reaction.



Entry	Base	t [h]	Yield [%]
1	LDA (1 equiv)	6	22
2	LDA (2 equiv)	6	63
3	NaHMDS (2 equiv)	6	38
4	LiHMDS (2 equiv)	6	31
5	KOtBu (2 equiv)	6	< 10
6	LDA (3 equiv)	4	77
7	LDA (3 equiv, Et_2O)	4	49
8	LDA (3 equiv, 0 °C)	4	0
9	LDA (3 equiv)	4	60[a]
10	LDA (3 equiv)	4	52[b]
11	LDA (3 equiv)	4	58[c]
12	LDA (3 equiv)	4	55[d]

Standard reaction conditions: Crotonate (1.2 equiv) added to base in THF at −78 °C followed by slow addition of a 1.0 M THF solution of imine (1.0 equiv; 0.5 mL h^{-1}). Only a single product diastereomer is observed by ^{1}H NMR analysis. [a] 1.0 mL h^{-1} addition of imine. [b] 2.0 mL h^{-1} addition of imine. [c] Imine and crotonate added simultaneously to a cooled LDA solution. [d] LDA added to solution of imine and crotonate at −78 °C. HMDS = hexamethyldisilazide, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

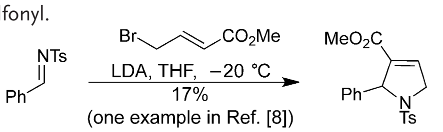
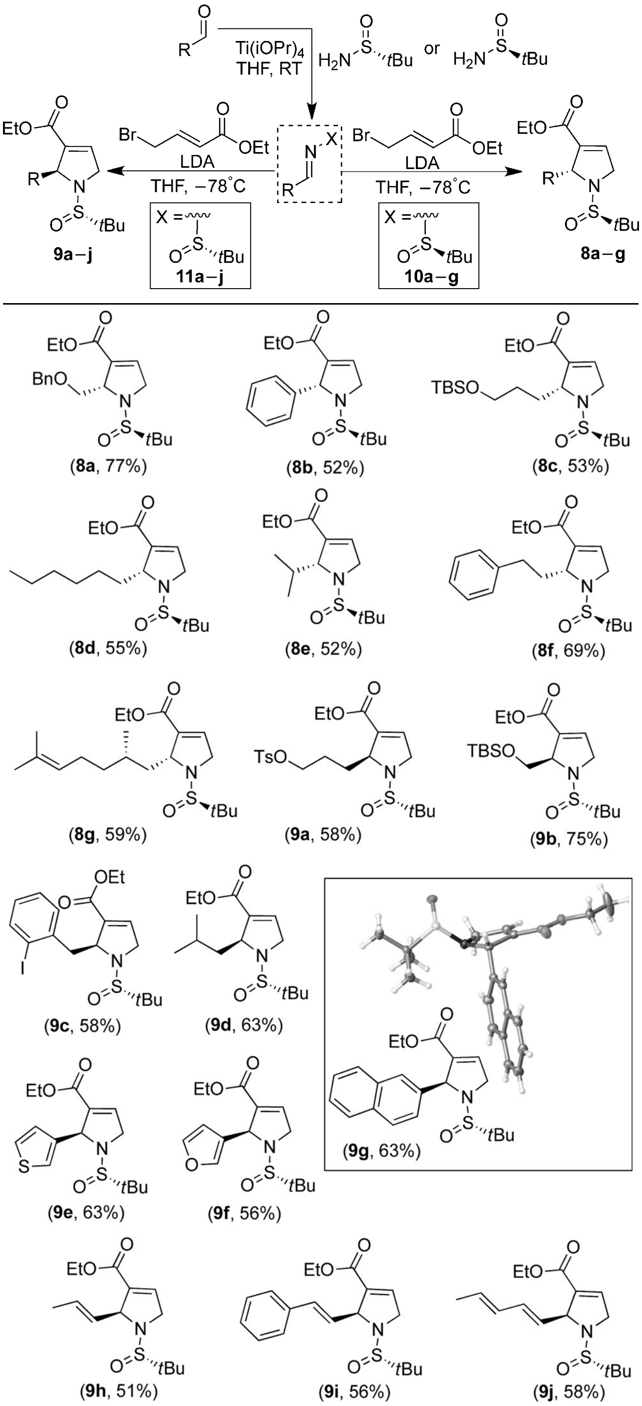


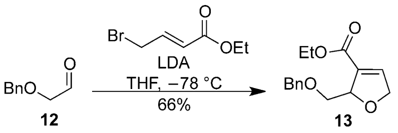
Table 2: [3+2] Annulation: Scope



Reaction conditions: LDA (3 equiv), crotonate (1.2 equiv), imine (1.0 equiv), THF, −78 °C. One 3-pyrroline diastereomer was observed in all cases. Thermal ellipsoids for **9g** shown at 50% probability.[20] TBS = *tert*-butyldimethylsilyl.

configuration of the other stereocenter is erased in the ensuing anionic isomerization and cyclization steps. A major strength of this method is the ready access to either 3-pyrroline enantiomeric series (**8a**–**g** and **9a**–**j**) by simply changing the imine auxiliary (**10a**–**g** and **11a**–**j**), which also serves the role of a nitrogen protecting group. Hindered imines, ethers, sulfonate esters, heteroaryl substituents, and conjugated imines are all well tolerated.

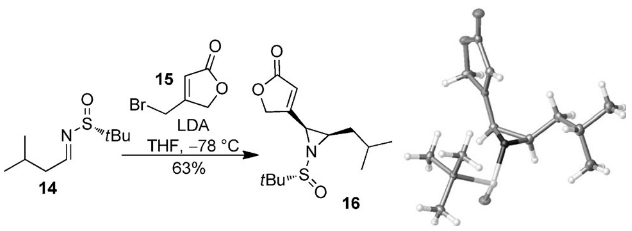
With the new asymmetric 3-pyrroline annulation reaction established, we wondered if this approach could also be applied to aldehydes. Although this type of reaction is not known for aldehydes, there are several reported examples of vinylogous Darzens reactions between aldehydes and halo crotonates to form vinyl oxiranes.[11] Toward that end, treatment of the aldehyde **12** with the enolate derived from ethyl 4-bromocrotonate (**1**), using our standard reaction conditions, afforded only the [3+2] annulation product **13** (Scheme 2). This constitutes a new scalable route to 2,5-dihydrofuran



Scheme 2. [3+2] Annulation works for an aldehyde.

products. Efforts are underway to explore the scope of this reaction and develop an asymmetric variant.

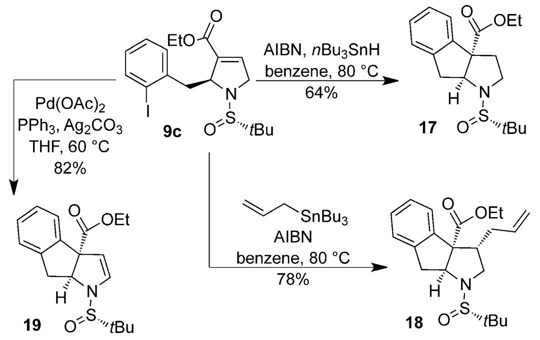
As mentioned in the introduction, we were surprised to find a dearth of literature on vinylogous aza-Darzens reactions, and no asymmetric examples. This finding inspired us to investigate whether a strategically substituted nucleophile could be used to divert the reaction to a γ-selective imine addition pathway, and thus to a vinyl aziridine product. For this purpose we chose the readily available 4-(bromomethyl)furan-2(5H)-one as the nucleophile (**15**: Scheme 3). By using our standard reaction conditions, the vinyl aziridine product **16** was obtained in very good yield, with none of the [3+2] annulation product being isolated. We were able to grow a high quality crystal of the product, thus allowing assignment of its relative and absolute configuration as the *cis*-vinyl aziridine shown. Unlike in the pyrroline case, we were able to establish that the Ellman auxiliary performed as expected and that the addition step was *syn*-selective. This fascinating and useful result provides insight into the sensitivity of the annulation to sterics and represents the only reported example of an asymmetric vinylogous aza-Darzens reaction. Efforts are underway to explore a wider range of nucleophiles to decipher the fine balance needed to funnel products to either annulation pathway.



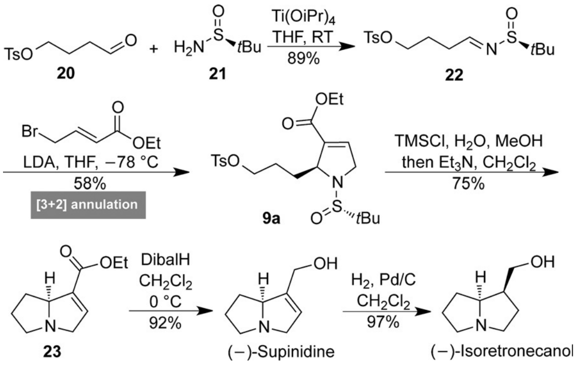
Scheme 3. Asymmetric vinylogous aza-Darzens reaction. Thermal ellipsoids for **16** shown at 50% probability.[20]

Presented in Scheme 4 are synthetic application examples of how the pyrroline product **9c** can be converted, in a substrate controlled manner, into valuable fused tricyclic architectures by exploiting the iodoaryl group. For example, a *5-exo*-trig radical cyclization can be either reductively terminated (**17**) or trapped with appropriate partners to forge an additional C−C bond (**18**). Palladium-mediated cyclization affords a useful 2-pyrroline moiety (**19**) for further functionalization. Such strategies are currently being used in our laboratory to build diverse collections of enantiopure nitrogen heterocycles.[12]

To highlight the power of this new asymmetric annulation reaction and to further demonstrate its compatibility with reactive functional groups (Scheme 5) we chose to pursue the pyrrolizidine alkaloids (−)-supinidine and (−)-isoretronecanol. As such, we formed the requisite imine (**22**) of an aldehyde containing a primary tosylate. This imine was shown to be a compatible substrate, thus affording the expected pyrroline product **9a**. The pyrrolizidine fused ring system **23** was then formed by removing the nitrogen protecting group and cyclizing the resulting amine using triethylamine. Reduction with diisobutylaluminum hydride afforded (−)-supinidine, whose spectral data and optical rotation matched that of the literature reports.[13] Substrate-controlled hydrogenation of (−)-supinidine completed an asymmetric total synthesis of (−)-isoretronecanol.[14] Our asymmetric total synthesis of (−)-supinidine was accomplished in only six steps from a commodity chemical, 1,4-butanediol. This route represents the shortest asymmetric synthesis of (−)-supinidine.

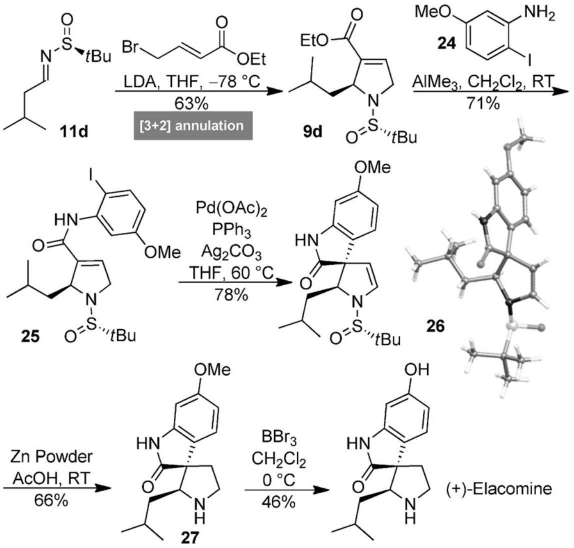


Scheme 4. Rapid access to fused nitrogen heterocyclic motifs. AIBN = 2,2′-azobis(2-methylpropionitrile).



Scheme 5. New approach to pyrrolizidine alkaloids. TMS = trimethylsilyl.

Elacomine is an intriguing spirooxindole natural product whose structure and absolute configuration was confirmed by Borschberg and co-workers.[15] Racemic elacomine has been synthesized three times, by the groups of Borschberg, Horne,[16] and White,[17] in addition to one formal synthesis by Takemoto and co-workers.[18] These syntheses use tryptamine-type starting materials and employ an acid-catalyzed step to form the spirooxindole core, which is a limitation if access to enantiopure material is desired. For example, Borschberg's racemic elacomine total synthesis required five steps, while his synthesis of (+)-elacomine, the only reported asymmetric synthesis, is eleven steps (76% *ee*).



Scheme 6. Asymmetric total synthesis of (+)-elacomine. Thermal ellipsoids for **26** shown at 50% probability.[20]

Takemoto's synthesis employs an acyl palladium cyclization strategy for the key step, but required eighteen steps. Presented in Scheme 6 is the shortest asymmetric total synthesis of (+)-elacomine, and it makes use of a substrate-controlled Heck cyclization step to form the spirooxindole core. We first treated the Ellman imine (**11d**) of isovaleraldehyde with the enolate of ethyl 4-bromocrotonate under our new annulation conditions. The ester of the resulting pyrroline (**9d**) was then converted into the iodo arylamide **25** using Weinreb's protocol and aniline **24**.[19] Heck cyclization to form the spirooxindole core (**26**) proceeded in very good yield and with complete substrate control as evident from X-ray crystallographic analysis. Interestingly, radical cyclization approaches failed to produce the spirooxindole, as did palladium cyclizations employing an aryl bromide. Treatment of the protected enamine functionality with zinc in acetic acid deprotected the nitrogen atom and reduced the resulting imine, thus affording the methoxy-protected elacomine **27**. Standard deprotection conditions then afforded (+)-elacomine in only six steps from isovaleraldehyde.

In summary, we report a new asymmetric [3+2] annulation reaction to form 3-pyrrolines. This new reaction is compatible with aryl, alkyl, and conjugated imines. The power of this new asymmetric method is highlighted with the shortest total syntheses of (+)-elacomine and (−)-supinidine. We have further demonstrated that this annulation approach can be applied to an aldehyde or alternatively be diverted to a vinyl aziridine by the increasing steric bulk of the nucleophile. Also reported is the first example of an asymmetric vinylogous aza-Darzens reaction.

Acknowledgements

We thank the NSF (CHE-1266365) for financial support of initial exploratory studies.

Keywords: annulation · heterocycles · reaction mechanisms · synthetic methods · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 13706–13710
Angew. Chem. **2015**, *127*, 13910–13914

---

[1] K. Ebitani in *Comprehensive Organic Synthesis II* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, Chap. 2.14, pp. 571–605.

[2] For a recent review of the aza-Darzens reaction, consult: J. Sweeney, *Eur. J. Org. Chem.* **2009**, 4911.

[3] F. A. Davis, P. Zhou, G. V. Reddy, *J. Org. Chem.* **1994**, *59*, 3243; for our studies, we employed the Ellman auxiliary: G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913.

[4] a) M. Brichacek, M. N. Villalobos, A. Plichta, J. T. Njardarson, *Org. Lett.* **2011**, *13*, 1110; b) M. Brichacek, D. Lee, J. T. Njardarson, *Org. Lett.* **2008**, *10*, 5023.

[5] Closest reported example is a racemic ylide approach: A.-H. Li, L.-X. Dai, X.-L. Hou, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2725; after we started our investigations a single low-yielding racemic aza-Darzens example was reported: A. N. Jarvis, A. B. McLaren, H. M. I. Osborn, J. Sweeney, *Beilstein J. Org. Chem.* **2013**, *9*, 852.

[6] Examples of recent synthetic approaches to 3-pyrrolines: M. Brichacek, J. T. Njardarson, *Org. Biomol. Chem.* **2009**, *7*, 1761; selected examples of different asymmetric strategies for forming 3-pyrrolines: a) A. I. Meyers, D. A. Dickman, T. R. Bailey, *J. Am. Chem. Soc.* **1985**, *107*, 7974; b) T. J. Donohoe, J.-P. Guillermin, C. Frampton, D. S. Walter, *Chem. Commun.* **2000**, 465; c) J. G. Breuil-Desvergnes, *Tetrahedron* **2001**, *57*, 1951; d) S. Kaden, H.-U. Reissig, *Org. Lett.* **2006**, *8*, 4763; e) Y.-Q. Fang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 5660; f) X. Han, F. Zhong, Y. Wang, Y. Lu, *Angew. Chem. Int. Ed.* **2012**, *51*, 767; *Angew. Chem.* **2012**, *124*, 791; and g) C. E. Henry, Q. Xu, Y. C. Fan, T. J. Martin, L. Belding, T. Dudding, O. Kwon, *J. Am. Chem. Soc.* **2014**, *136*, 11890.

[7] Dienolates of esters have been investigated extensively. For a review focusing on carbonyl trapping, consult: G. Casiraghi, F. Zanardi, G. Appendino, G. Rassu, *Chem. Rev.* **2000**, *100*, 1929.

[8] D. J. Aldous, A. S. Batsanov, D. S. Yugit, A. J. Dalencon, W. M. Dutton, P. G. Steel, *Org. Biomol. Chem.* **2006**, *4*, 2912.

[9] L. B. Schenkel, J. A. Ellman, *Org. Lett.* **2004**, *6*, 3621.

[10] G. Liu, D. A. Cogan, T. D. Owens, T. P. Tang, J. A. Ellman, *J. Org. Chem.* **1999**, *64*, 1278.

[11] Vinylogous Darzen reactions to form vinyl oxiranes are known: a) V. F. Martynov, E. I. Strygin, *Zh. Org. Khim.* **1966**, *2*, 1319; b) G. A. Koppel, *Tetrahedron Lett.* **1972**, *13*, 1507; interestingly, in this publication, Koppel proposes the possibility of the 2,5-dihydrofuran product but does not observe any under his reaction conditions; c) W. Eberbach, B. Burchardt, *Chem. Ber.* **1978**, *111*, 3665; d) D. J. Aldous, A. J. Dalencon, P. G. Steel, *Org. Lett.* **2002**, *4*, 1159.

[12] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[13] Total syntheses of (−)-supinidine: a) D. J. Robins, S. Sakdarat, *J. Chem. Soc. Chem. Commun.* **1979**, 1181; b) H. Rueger, M. Benn, *Heterocycles* **1982**, *9*, 1677; c) Y. Nagao, W.-M. Dai, M. Ochiai, *Tetrahedron Lett.* **1988**, *29*, 6133; d) H. Takahata, Y. Banba, T. Momose, *Tetrahedron* **1991**, *47*, 7635; e) A. Hassner, S. Singh, R. Sharma, R. Maurya, *Tetrahedron* **1993**, *49*, 2317; f) C. M. Boynton, A. T. Hewson, D. Mitchell, *J. Chem. Soc. Perkin Trans. 1* **2000**, 3599.

[14] Total syntheses of (−)-isoretronecanol: a) K. Tatsuta, H. Takahashi, Y. Amemiya, M. Kinoshita, *J. Am. Chem. Soc.* **1983**, *105*, 4096; b) T. Morikawe, S.-I. Hamano, S. Saito, *Heterocycles* **1988**, *27*, 1125; c) J. G. Knight, S. V. Ley, *Tetrahedron Lett.* **1991**, *32*, 7119; d) G. Haviari, J. P. Celerier, H. Petit, G. Lhommet, *Tetrahedron Lett.* **1993**, *34*, 1599; e) D. W. Knight, A. C. Share,

P. T. Gallagher, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2089; f) P.-O. Delaye, T. K. Pradhan, E. Lambert, J.-L. Vase, J. Szymoniak, *Eur. J. Org. Chem.* **2010**, 3395; g) K. K. S. Reddy, B. V. Rao, S. S. Raju, *Tetrahedron: Asymmetry* **2011**, *22*, 662; h) M. Brambilla, S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Tetrahedron* **2014**, *70*, 204.

[15] C. Pellegrini, M. Weber, H.-J. Borschberg, *Helv. Chim. Acta* **1996**, *79*, 151 and references therein.

[16] F. Y. Miyake, K. Yakushijin, D. A. Horne, *Org. Lett.* **2004**, *6*, 711.

[17] J. D. White, Y. Li, D. C. Yhle, *J. Org. Chem.* **2010**, *75*, 3569.

[18] H. Kamisaki, T. Nanjo, C. Tsukano, Y. Takemoto, *Chem. Eur. J.* **2011**, *17*, 626.

[19] M. F. Lipton, A. Basha, S. M. Weinreb, *Org. Synth.* **1979**, *59*, 49.

[20] CCDC 1062144 (**9g**), 1062145 (**16**), and 1062146 (**26**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Received: July 15, 2015
Revised: September 12, 2015