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Total Synthesis

Synthesis of the *Strychnos* Alkaloid (−)-Strychnopivotine and Confirmation of its Absolute Configuration

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Abstract: The first enantioselective synthesis of (−)-strychnopivotine from a known and inexpensive phenol has been achieved in 15 steps. The strategy is based on a new diastereoselective aza-Michael-enol-ether cascade desymmetrization of a dienone, guided by a removable lactic acid-derived chiral auxiliary. Synthesis involves a phenol dearomatization, a conjugated silicon addition, a stereoselective double reductive amination, and two Heck-type carbopalladations as key steps. The absolute configuration of the natural compound, which, to date, has been uncertain, was confirmed by using circular dichroism (CD) spectroscopy and X-ray analyses.

Strychnopivotine **1** (see Figure 1), a pentacyclic *Strychnos* alkaloid[1] from the curan family, was first isolated by the group of

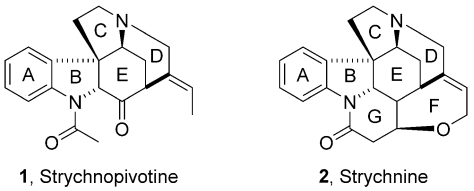
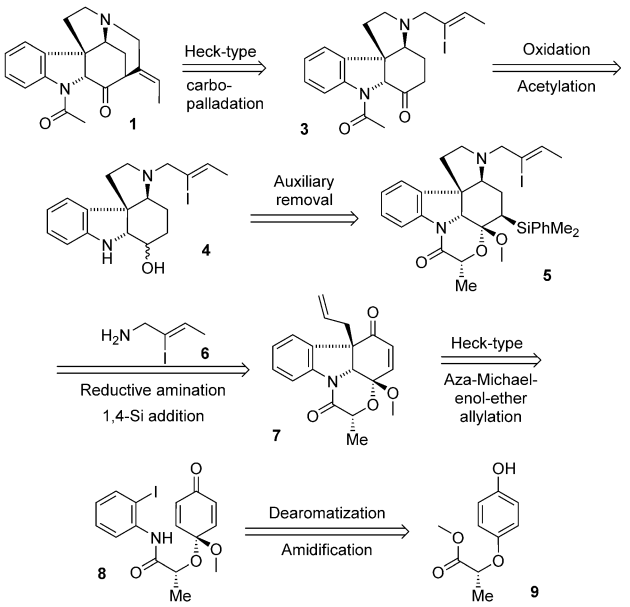


Figure 1. Strychnopivotine and strychnine, two *Strychnos* alkaloids.

Angenot in 1980 from the root bark of *Strychnos variabilis*.[2] However, to date, the absolute configuration of strychnopivotine has been uncertain, due to the absence of X-ray crystal structure analyses of the natural compound. Despite its unusual structure and, unlike others alkaloids from this family, such as strychnine **2**,[3,4] strychnopivotine has received little attention from the scientific community. Indeed, its biological activity has not been evaluated, and although some efforts towards the construction of its core structure have been reported,[5] only one total synthesis of (±)-strychnopivotine has been achieved, by the leading group of Padwa in 2008.[6] Their strategy employed a noteworthy [4+2]-cycloaddition/rearrangement cascade to produce the ABCE substructure of the natural compound. However, an enantioselective synthetic route to strychnopivotine is still required to validate its absolute configuration and enable further research on the biological activity of this compound and its analogs. Our interest in the total synthesis of natural products through oxidative dearomatization[7] led us to develop an asymmetric pathway to strychnopivotine, which is reported in this communication.

Our retrosynthetic analysis began with intramolecular carbopalladation to close the D ring from iodoalkene **3** (Scheme 1).



Scheme 1. Retrosynthesis of (−)-strychnopivotine.

The latter can be obtained by acetylation of indoline **4**, which can be produced by hydrolysis of the chiral auxiliary of **5**. The C ring can be created by stereoselective double reductive amination using amine **6**[8] from **7**. The B ring can be constructed by diastereoselective desymmetrization of dienone **8** via an aza-Michael-enol-ether tandem process followed by Heck-type coupling. The latter can be generated by amidification of ester **9** and phenol dearomatization.

Synthesis began with the treatment of the known ester **9** with the aluminum salt of 2-iodoaniline to produce amide **10** (87%; see Scheme 2).[9] The latter was used in oxidative dearomatization[10] mediated by a hypervalent iodine reagent, as demonstrated by Kita and co-workers,[11] to generate dien-

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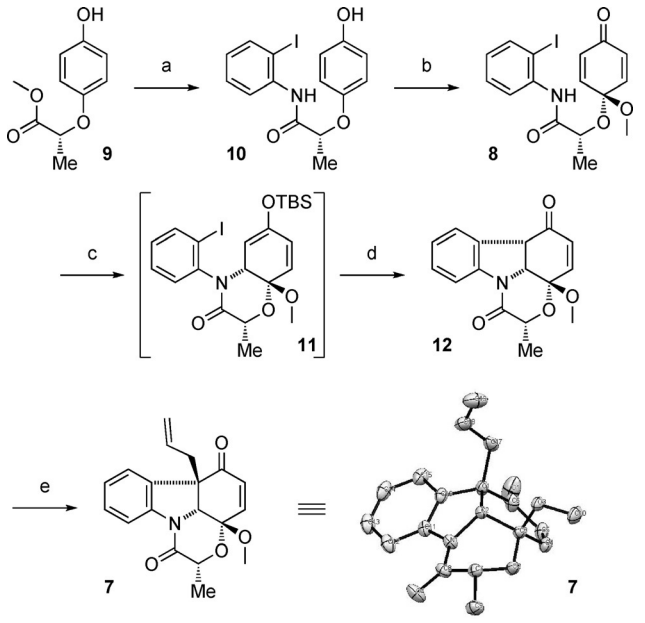
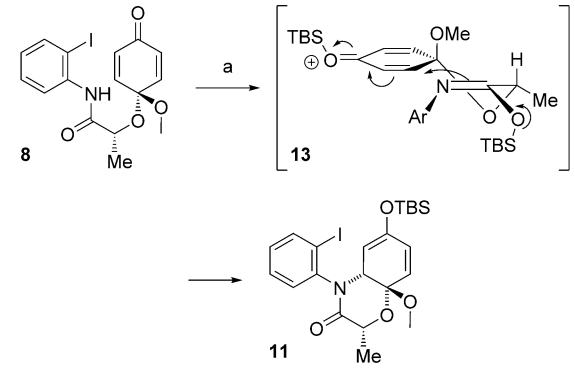


Scheme 2. Synthesis of the key tetracyclic intermediate **12** through an aza-Michael-enol-ether tandem process, and ORTEP representation of **7**. Reaction conditions: a) 2-iodoaniline, DIBAL-H, THF, 0 °C to RT, 12 h, 87%; b) DIB, MeOH, 0 °C, 5 min, 89%; c) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to RT, 12 h; d) $Pd(PPh_3)_4$, Et_3N, CH_3CN, reflux, 12 h, 70% over two steps, 1:19 d.r.; e) KHMDS, allylbromide, THF, −78 °C to 0 °C, 1 h, 75%. DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran, DIB = (diacetoxyiodo)benzene, TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, KHMDS = potassium bis(trimethylsilyl)amide.

one **8** (89%). Subsequently, **8** was treated by using a novel diastereoselective aza-Michael-enol-ether tandem process to produce **11**. This method completes other noteworthy processes that have been developed in the search for asymmetric pathways leading to chiral cyclohexenones.[12] This transformation is our key step in desymmetrizing dienone **8** and developing asymmetric synthesis of this target. The lactic acid-derived moiety present on the lateral chain is used as a chiral auxiliary that will later be removed. TBS-activation produces an enol-ether that is essential for this process, being an ideal Heck-type acceptor to yield the indoline ring of strychnopivotine by a carbopalladation strategy. This step delivered tetracycle **12** in 70% yield over two steps and at a minimum of 1:19 d.r. within the limits of NMR at 300 MHz. Finally, regio- and stereoselective allylation of **12** under classical conditions yielded the key intermediate **7** (75%), which contains the quaternary carbon center of strychnopivotine. Crystallographic analysis of **7** confirmed its absolute configuration, depicted in Scheme 2.

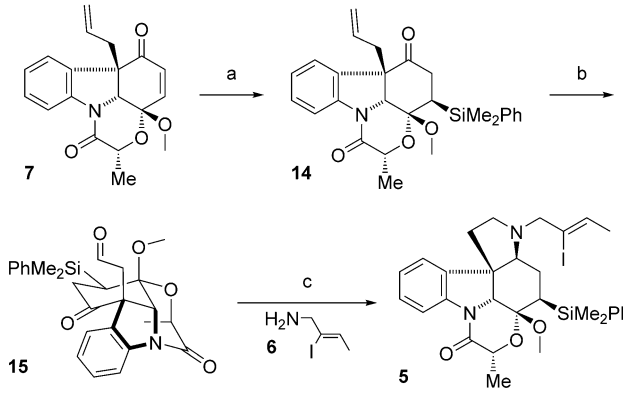
To explain the stereoselectivity of the desymmetrization, we hypothesized that the transformation involved the formation of imino-ether **13** (Scheme 3). The nitrogen atom then attacked the activated Michael acceptor on the face it was tethered through a half-chair transition state, in which the methyl group of the chiral auxiliary was located equatorially to minimize steric interactions.

At this stage, it was necessary to prepare the molecule for construction of the C ring. To this end, we envisaged the introduction of a bulky and removable functional group by a conju-



Scheme 3. Proposed mechanism for formation of **11**. Reaction conditions: a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C to RT, 12 h, 70%. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

gated addition onto enone **7**. This addition might force the molecule to further adopt a favorable transition state, in which the hydride must approach on the required (*Re*)-face, thereby directing a reductive amination and leading to the formation of the desired diastereoisomer **5**. Therefore, Michael acceptor **7** was reacted with a silicon-based cuprate developed by Fleming and co-workers[13] to generate the silylated compound **14** in 63% as the sole diastereoisomer (Scheme 4). The *cis* rela-

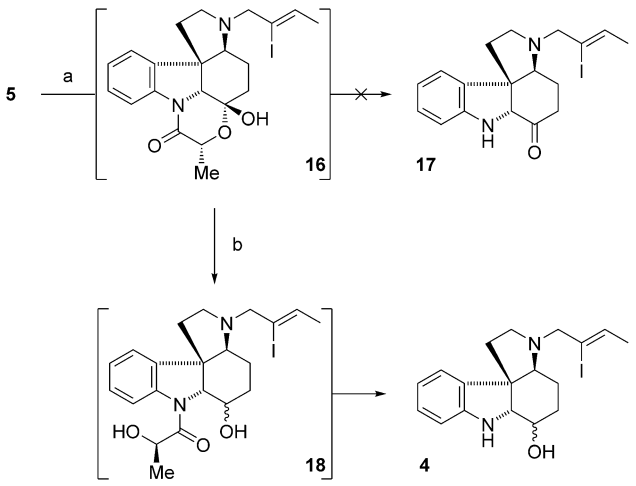


Scheme 4. Installation of the C ring of strychnopivotine. Reaction conditions: a) $(PhMe_2Si)_2CuLi$, THF, −78 °C, 1 h, 63%; b) O_3, MeOH, −78 °C, 10 min, then PPh_3, MeOH, RT, 1 h; c) **6**, $NaBH_3CN$, cat. AcOH, MeOH, 0 °C to RT, 1 h, 63% over two steps.

tionship between the methoxy and silylated groups was determined by NOE NMR. A subsequent ozonolysis converted the olefin into the corresponding aldehyde **15**, which was directly submitted to the reductive amination conditions involving primary amine **6** in the presence of $NaBH_3CN$ as a reductant and acetic acid as a catalyst. Under these conditions, compound **5** exhibiting the desired *cis* CE ring junction was generated as a single diastereoisomer (confirmed by NMR at 300 MHz) in 63% over two steps.

To close the final ring of the target and complete the synthesis, the chiral auxiliary and silylated group had to be removed. To this end, we first considered an acidic aqueous hydrolysis. However, although simple treatment of **5** with

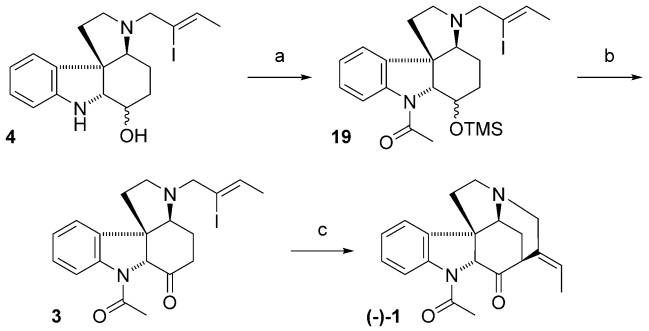
concentrated aqueous HCl allowed us to hydrolyze the ketal function and remove the silylated functional group (Scheme 5), no traces of **17** were observed. Modification of the experimental conditions, such as pH (including basic conditions), choice of acid, reaction time or temperature, mostly resulted in degradation of the molecule. Further experiments, such as nucleophilic attacks on the acetamide, also failed to produce the desired intermediate **17**. On this basis, we hypothesized that the auxiliary was trapped in a hindered hemi-ketal-lactam arrangement, and was thus resistant to removal. To open the blocked form and enable amide hydrolysis, we proposed to reduce the hemi-ketal **16** selectively to the corresponding alcohol. Interestingly, when **16** was treated with $NaBH_4$ in ethanol, we observed complete and facile removal of the auxiliary during the reduction—probably due to the presence of sodium ethoxide—leading to an epimeric mixture of alcohols **4** in 85% yield over two steps.



Scheme 5. Removal of the chiral auxiliary. Reaction conditions: a) Conc. HCl, 1:1 AcOH/H_2O, 50 °C, 1 h; b) $NaBH_4$, EtOH, 0 °C to RT, 12 h, 85% over two steps.

Alcohol mixture **4** was protected with a TMS group under classical conditions, and acetamide **19** was produced using acetyl chloride and pyridine (Scheme 6). Deprotection under mild acidic conditions followed by Ley–Griffith oxidation[14] of the mixture of alcohols converged on the intermediate **3** in 52% yield over four steps, including one-pot procedures. With this direct precursor in hand, the D ring was finally closed by a Heck-type coupling involving $PdCl_2(dppf)\cdot CH_2Cl_2$ in basic conditions.[15] A large amount of methanol solvent is required to avoid the formation of an enolate on the acetamide moiety, which could trigger undesired side reactions (e.g., migration of the acetyl group), as judiciously described by Padwa and co-workers.[6] Those conditions allowed us to complete the first asymmetric synthesis of Strychnopivotine in 20% yield.

Circular dichroism (CD) spectroscopy of our synthetic (−)-**1** displayed a positive Cotton effect at 253 nm ($\Delta\varepsilon_{(253)} \approx +28.5$) and a negative Cotton effect at 298 nm ($\Delta\varepsilon_{(298)} \approx -10$).[16] These values are sufficiently close to the literature values ($\Delta\varepsilon_{(252)} = +28.8$ and $\Delta\varepsilon_{(298)} = -8.8$)[2] to allow a high degree of confidence that our synthetic (−)-strychnopivotine is the same enantiomer as the extracted strychnopivotine. Moreover, crystallographic analysis of **7** confirmed that the absolute configuration of the natural strychnopivotine was the one proposed by Angenot and co-workers.[2]



Scheme 6. Completion of synthesis of (−)-strychnopivotine. Reaction conditions : a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 10 min; then AcCl, pyridine, CH_2Cl_2, 0 °C to RT, 30 min; b) TsOH, MeOH, RT, 30 min; then TPAP, NMO, CH_3CN, RT, 1 h, 52% over four steps; c) $PdCl_2(dppf)\cdot CH_2Cl_2$, K_2CO_3, MeOH, 70 °C, 10 min, 20%. TMSOTf = trimethylsilyl trifluoromethanesulfonate, TPAP = tetrapropylammonium perruthenate, NMO = N-methylmorpholine-*N*-oxide, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

In summary, we achieved the enantioselective synthesis of (−)-strychnopivotine in 15 steps from a simple and inexpensive phenol. The most innovative step of the synthesis was a novel diastereoselective aza-Michael-enol-ether cascade desymmetrization of a dienone system, guided by a removable lactic acid-derived chiral auxiliary. The synthesis included dearomatization of a phenol mediated by a hypervalent iodine reagent, stereoselective conjugated Si addition, stereoselective double reductive amination, and two Heck-type carbopalladations. CD spectroscopy and X-ray crystal structure analyses confirmed the absolute configuration of the natural extracted compound.

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[1] a) J. Bosch, J. Bonjoch, M. Amat in *The Alkaloids, Vol. 48* (Ed.: G. A. Cordell), Academic Press, New York, **1996**, pp. 75–189; b) J. Sapi, G. Massiot in *Monoterpenoid Indole Alkaloids* (Ed.: J. E. Saxton) in *The Chemistry of Heterocyclic Compounds* (Ed. E. C. Taylor), Wiley, New York, **1994**, Supp. to Vol. 25, part 4, pp. 5213–5216.

[2] M. Tits, D. Tavernier, L. Angenot, *Phytochemistry* **1980**, *19*, 1531.

[3] For a review about syntheses of Strychnine, see: J. S. Cannon, L. E. Overman, *Angew. Chem. Int. Ed.* **2012**, *51*, 4288; *Angew. Chem.* **2012**, *124*, 4362.

[4] a) P. Magnus, M. Giles, R. Bonnert, C. S. Kim, L. McQuire, A. Merritt, N. Vicker, *J. Am. Chem. Soc.* **1992**, *114*, 4403; b) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293; c) M. E. Kuehne, F. Xu, *J. Org. Chem.* **1993**, *58*, 7490; d) V. H. Rawal, S. Iwasa, *J. Org. Chem.* **1994**, *59*, 2685; e) M. E. Kuehne, F. Xu, *J. Org. Chem.* **1998**, *63*, 9427; f) D. Solé, J. Bonjoch, S. García-Rubio, E. Peidró, J. Bosch, *Angew. Chem. Int. Ed.* **1999**, *38*, 395; *Angew. Chem.* **1999**, *111*, 408; g) M. Ito, C. W. Clark, M. Mortimore, J. B. Goh, S. F. Martin, *J. Am. Chem. Soc.* **2001**, *123*, 8003; h) M. J. Eichberg, R. L. Dorta, K. Lamottke, K. P. C. Vollhardt, *Org. Lett.* **2000**, *2*, 2479; i) M. Nakanishi, M. Mori, *Angew. Chem. Int. Ed.* **2002**, *41*, 1934; *Angew. Chem.* **2002**, *114*, 2014; j) G. J. Bodwell, J. Li, *Angew. Chem. Int. Ed.* **2002**, *41*, 3261; *Angew. Chem.* **2002**, *114*, 3395; k) T. Ohshima, Y. Xu, R. Takita, S. Shimuzu, D. Zhong, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 14546; l) Y. Kaburagi, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc.* **2004**, *126*, 10246; m) H. Zhang, J. Boonsombat, A. Padwa, *Org. Lett.* **2007**, *9*, 279; n) G. Sirasani, T. Paul, W., Jr. Dougherty, S. Kassel, R. B. Andrade, *J. Org. Chem.* **2010**, *75*, 3529; o) C. Beemelmanns, H. U. Reissig, *Angew. Chem. Int. Ed.* **2010**, *49*, 8021; *Angew. Chem.* **2010**, *122*, 8195; p) D. B. C. Martin, C. D. Vanderwal, *Chem. Sci.* **2011**, *2*, 649; q) S. B. Jones, B. Simmons, A. Mastracchio, D. W. C. MacMillan, *Nature* **2011**, *475*, 183; r) J. Bonjoch, D. Solé, *Chem. Rev.* **2000**, *100*, 3455; s) M. Mori, *Heterocycles* **2010**, *81*, 259; t) L. Furst, C. R. Stephenson, *Nat. Chem. Biol.* **2011**, *7*, 582; u) C. Beemelmanns, H. U. Reissig, *Chem. Soc. Rev.* **2011**, *40*, 2199; v) D. B. C. Martin, L. Q. C. Nguyen, D. Vanderwal, *J. Org. Chem.* **2012**, *77*, 17; w) C. Beemelmanns, H. U. Reissig, *Chem. Rec.* **2015**, *15*, 872.

[5] H. J. Teuber, C. Tsaklakidis, J. W. Bats, *Liebigs Ann. Chem.* **1992**, 461; D. Solé, X. Urbaneja, A. Cordero-Vargas, J. Bonjoch, *Tetrahedron* **2007**, *63*, 10177.

[6] J. Boonsombat, H. Zhang, M. Chughtai, J. Hartung, A. Padwa, *J. Org. Chem.* **2008**, *73*, 3539.

[7] a) K. C. Guérard, V. Hamel, A, Guérinot, C. Bouchard-Aubin, S. Canesi, *Chem. Eur. J.* **2015**, *21*, 18068; b) G. Jacquemot, G. Maertens, S. Canesi, *Chem. Eur. J.* **2015**, *21*, 7713; c) G. Maertens, C. L'Homme, S. Canesi, *Front. Chem.* **2015**, *2*, 115; d) S. Desjardins, G. Maertens, S. Canesi, *Org. Lett.* **2014**, *16*, 4928; e) C. L'Homme, M.-A. Ménard, S. Canesi, *J. Org. Chem.* **2014**, *79*, 8481; M. A. Beaulieu, X. Ottenwaelder, S. Canesi, *Chem. Eur. J.* **2014**, *20*, 7581; f) K. C. Guérard, A. Guérinot, C. Bouchard-Aubin, M. A. Ménard, M. Lepage, M. A. Beaulieu, S. Canesi, *J. Org. Chem.* **2012**, *77*, 2121; g) M. A. Beaulieu, K. C. Guérard, G. Maertens, C. Sabot, S. Canesi, *J. Org. Chem.* **2011**, *76*, 9460; h) M. A. Beaulieu, C. Sabot, N. Achache, K. C. Guérard, S. Canesi, *Chem. Eur. J.* **2010**, *16*, 11224; i) C. Sabot, K. C. Guérard, S. Canesi, *Chem. Commun.* **2009**, 2941; j) K. C. Guérard, C. Sabot, L. Racicot, S. Canesi, *J. Org. Chem.* **2009**, *74*, 2039; k) C. Sabot, D. Bérard, S. Canesi, *Org. Lett.* **2008**, *10*, 4629.

[8] a) P. Liu, J. Wuang, J. Zhang, F. G. Qiu, *Org. Lett.* **2011**, *13*, 6426; b) M. E. Krafft, J. W. Cran, *Synlett* **2005**, 1263.

[9] P. Q. Huang, X. Zheng, X.-M. Deng, *Tetrahedron Lett.* **2001**, *42*, 9039.

[10] a) S. Quideau, M. A. Looney, L. Pouységu, *Org. Lett.* **1999**, *1*, 1651; b) M. Traoré, S. Ahmed-Ali, M. Peuchmaur, Y. S. Wong, *Tetrahedron* **2010**, *66*, 5863; c) H. Liang, M. A. Ciufolini, *Tetrahedron* **2010**, *66*, 5884; d) L. Pouységu, T. Sylla, T. Garnier, L. B. Rojas, J. Charris, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 5908; e) T. Jen, B. A. Mendelsohn, M. A. Ciufolini, *J. Org. Chem.* **2011**, *76*, 728; f) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235; g) M. Traoré, S. Ahmed-Ali, M. Peuchmaur, Y. S. Wong, *J. Org. Chem.* **2011**, *76*, 1409; h) L. Pouységu, M. Marguerit, J. Gagnepain, G. Lyvinec, A. J. Eatherton, S. Quideau, *Org. Lett.* **2008**, *10*, 5211; i) A. Ozanne-Beaudenon, S. Quideau, *Angew. Chem. Int. Ed.* **2005**, *44*, 7065; *Angew. Chem.* **2005**, *117*, 7227; j) J. Singh, F. V. Rehbein, T. Wirth, *ChemistryOpen* **2012**, *1*, 245; k) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018; *Angew. Chem.* **2013**, *125*, 7156; l) V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester, **2013**; m) P. Mizar, A. Laverny, M. El-Sherbini, U. Farid, M. Brown, F. Malmedy, T. Wirth, *Chem. Eur. J.* **2014**, *20*, 9910; n) V. Singh, T. Wirth, *Chem. Asian J.* **2014**, *9*, 950; o) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; p) A. Yoshimura, K. R. Middleton, A. D. Todora, B. J. Kastern, S. R. Koski, A. V. Maskaev, V. V. Zhdankin, *Org. Lett.* **2013**, *15*, 4010; q) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404; r) R. Leon, A. Jawalekar, T. Redert, M. J. Gaunt, *Chem. Sci.* **2011**, *2*, 1487.

[11] a) Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem.* **1987**, *52*, 3927; b) Y. Kita, H. Tohma, K. Hatanaka, T. Takada, S. Fujita, S. Mitoh, H. Sakurai, S. Oka, *J. Am. Chem. Soc.* **1994**, *116*, 3684; c) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem. Int. Ed.* **2008**, *47*, 3787; *Angew. Chem.* **2008**, *120*, 3847; d) T. Dohi, Y. Kita, *Chem. Commun.* **2009**, 2073; e) T. Dohi, M. Itob, N. Yamaokaa, K. Morimotoa, H. Fujiokab, Y. Kita, *Tetrahedron* **2009**, *65*, 10797; f) T. Dohi, N. Yamaoka, Y. Kita, *Tetrahedron* **2010**, *66*, 5775; g) T. Dohi, D. Kato, R. Hyodo, D. Yamashita, M. Shiro, Y. Kita, *Angew. Chem. Int. Ed.* **2011**, *50*, 3784; *Angew. Chem.* **2011**, *123*, 3868; h) K. Yasuyuki, D. Toshifumi, M. Eisuke, Y. Daisuke, M. Keitaro, *Heterocycles* **2014**, *88*, 245.

[12] a) P. Wipf, Y. Kim, *Tetrahedron Lett.* **1992**, *33*, 5477; b) P. Wipf, Y. Kim, D. Goldstein, *J. Am. Chem. Soc.* **1995**, *117*, 11106; c) P. Wipf, W. Li, *J. Org. Chem.* **1999**, *64*, 4576; d) P. Wipf, D. A. Mareska, *Tetrahedron Lett.* **2000**, *41*, 4723; e) P. Wipf, J. L. Methot, *Org. Lett.* **2000**, *2*, 4213; f) T. A. Wenderski, C. Hoarau, L. Mejorado, T. R. R. Pettus, *Tetrahedron* **2010**, *66*, 5873; g) G. Maertens, M. A. Ménard, S. Canesi, *Synthesis* **2014**, *46*, 1573.

[13] D. J. Ager, I. Fleming, S. K. Patel, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2520.

[14] a) W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc. Chem. Commun.* **1987**, 1625; b) S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.

[15] a) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, *130*, 5368; b) D. Solé, E. Peidró, J. Bonjoch, *Org. Lett.* **2000**, *2*, 2225; c) D. Solé, J. Diaba, J. Bonjoch, *J. Org. Chem.* **2003**, *68*, 5746; d) J. Bonjoch, F. Diaba, G. Puigbó, E. Peidró, D. Solé, *Tetrahedron Lett.* **2003**, *44*, 8387; e) D. Solé, X. Urbaneja, J. Bonjoch, *Adv. Synth. Catal.* **2004**, *346*, 1646; f) D. Solé, X. Urbaneja, J. Bonjoch, *Org. Lett.* **2005**, *7*, 5461.

[16] The CD spectrum is given in the Supporting Information.

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