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A Novel Short Convergent Entry into Himbacine Derivatives

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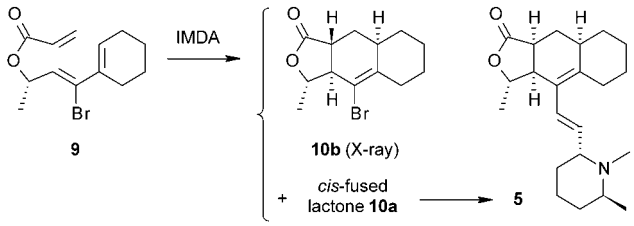
ABSTRACT



The IMDA reaction of 9 leads with good stereoselectivity to *exo*-adduct 10b. The functionalized ABC-ring core in 10 is well suited for the convergent synthesis of analogues of himbacine, a naturally occurring M_2 selective muscarine receptor antagonist, as illustrated with the further synthesis of the dehydro-derivative 5.

Among the piperidine alkaloids that were isolated 46 years ago from the bark of *Galbulimima baccata*, a species of the magnolia family found in New Guinea and parts of Australia, himbacine (**1**), himbeline (**2**), himandravine (**3**), and himgravine (**4**) possess an interesting tetracyclic structure, basically consisting of an ABC-ring part to which is connected, by an (*E*)-double bond, a 2,6-disubstituted piperidine D-ring.[1] These natural derivatives have been recent targets for total synthesis,[2,3] in particular when it became known that himbacine is a potent muscarinic receptor antagonist with selectivity for the M_2 receptor.[4] Since the blocking of presynaptic muscarinic receptors may contribute to the treatment of diseases in which the central cholinergic system degenerates,[5] the development of highly selective and potent M_2 antagonists is desirable.[6] So far structure−function relationship studies have shown that the deletion of substan-

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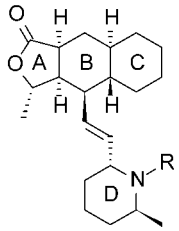
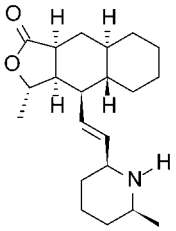
tial parts of the skeleton and/or functionality results in loss of affinity and/or selectivity.[6] Hence we became interested in the synthesis of substances that are isomeric with the natural derivatives.[2d] In this context we wish to describe here a short convergent approach that is well suited for analogue development, as illustrated with the enantioselective synthesis of (−)-dehydrohimbacine (**5**).



1 R = Me
2 R = H



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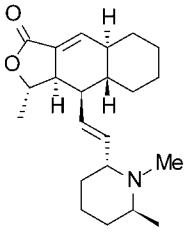

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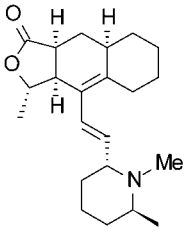
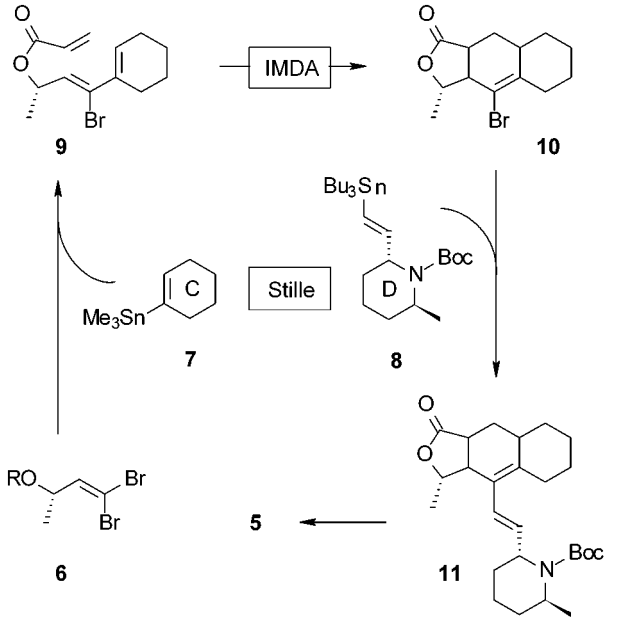


5

As shown in Scheme 1 our synthetic strategy rests on two key transformations. First, an intramolecular Diels−Alder reaction (IMDA)[7] involving a substituted pentadienyl acrylate to provide in a single step the required unsaturated ABC-ring skeleton (**9** to **10**). Second, attachment of the D-ring involving a Stille cross-coupling reaction to yield the required diene (**10** to **11**).[8] The latter reaction type is also used in the construction of the Diels−Alder precursor **9**. Hence central in the synthesis stands a geminal substituted dibromo alkene (**6**), the halogen atoms in which are both used in establishing key C−C bonds via palladium-catalyzed cross-coupling reactions with the vinylstannanes **7** and **8**. So far the Diels−Alder cycloaddition has been the preferred pathway for the synthesis of the ABC-ring skeleton.[2,3] Indeed, among the four different reported strategies,[2a−d] one involves an intermolecular cycloaddition[2c] and the others proceed via intramolecular versions centering around two different bond constructions. The present approach constitutes a third unprecendented construction set.

Scheme 1



The synthesis of (−)-**5** is outlined in Scheme 2.[9] The enantioselective preparation of Diels−Alder precursor **9** starts with (*S*)-ethyl lactate, which is converted to the geminal substituted dibromide **6** via a three-step sequence involving protection of the hydroxy group as *tert*-butyldimethylsilyl ether (**12**), reduction of the ester to the aldehyde **13**, and subsequent olefination to **6** (59% overall).[10] The first Stille coupling in the scheme involves reaction of **6** with vinylstannane **7**.[11] The use of the Stille reaction in the stereospecific conversion of 1,1-dibromo-1-alkenes with vinylstannanes to yield (*Z*)-monobromides has been studied in detail by Shen and Wang.[12] By using their optimized conditions (Pd_2dba_3 7 mol %, tris(2-furyl)phosphine (TFP), toluene, reflux, 4 h), bromodiene **15** is obtained in 71% yield. After further deprotection to alcohol **16**, the latter is converted to the required acrylate (68% yield).

The projected Diels−Alder reaction (**9** to **10**) involves as precursor a 3-bromo-4,5-dialkylpentadienyl acrylate carrying a stereocenter at the allylic 1-position of the tether. In practice when **9** is heated at 185 °C for 22 h (toluene, TEMPO, DIPEA), a mixture of two among the four possible adducts is obtained next to some starting material (8%). After chromatographic purification, the two adducts, **10a** and **10b** are obtained in 11% and 68% isolated yield, respectively. The unambiguous structural assignment of both adducts follows from (1) the X-ray crystallographic determination of the structure of crystalline **10b** revealing a *trans*-fused γ-lactone (Figure 1)[13] and (2) the observation that, upon basic treatment, **10b** isomerizes to adduct **10a** with a more stable *cis*-fused γ-lactone. This experimental result is in accord with

(7) For reviews on the IMDA reaction, see: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (b) Ciganek, E. *Org. React.* **1984**, *32*, 1. (c) Craig, D. *Chem. Soc. Rev.* **1987**, 187. (d) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 513.

(8) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.

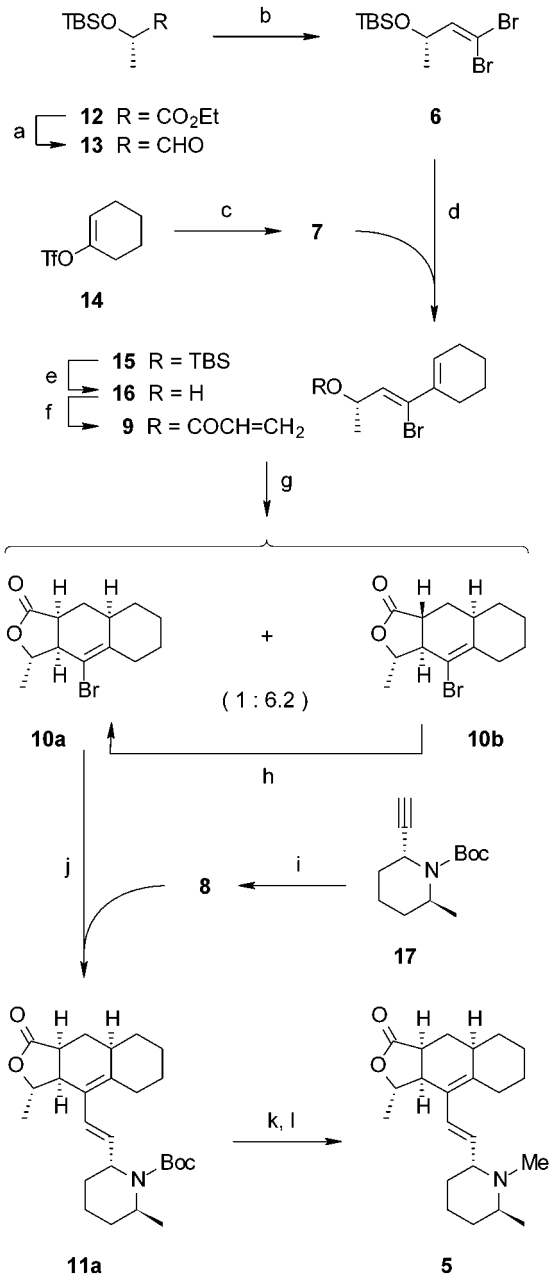
(9) All intermediates were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectroscopic methods.

(10) (a) Trost, B. M.; Mueller, T. J. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985. (b) Ku, Y.-Y.; Patel, R. R.; Elisseou, E. M; Sawick, D. *Tetrahedron Lett.* **1995**, *36*, 2733. (c) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230.

(11) The synthesis of cyclohexenyltrimethylstannane (**7**) involves the Pd(0)-catalyzed reaction of 1-cyclohexenyl triflate and hexamethylditin (Pd(Ph_3)$_4$, LiCl, THF, 60 °C, 79% yield), according to: Wulff, W. D.; Peterson, G. A.; Banta, W. E.; Chan, K. S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.

(12) (a) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. See also: (b) Uenishi, J.; Matsui, K. *Tetrahedron Lett.* **2001**, *42*, 4353.

Scheme 2[a]



[a] Reaction conditions: (a) DIBAL-H, toluene, −78 °C (80%); (b) PPh_3, CBr_4, CH_2Cl_2, −78 °C (78%); (c) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, LiCl, THF, 60 °C (84%); (d) Pd_2dba_3 (0.07 equiv), TFP (0.3 equiv), toluene, 110 °C, 4 h (71%); (e) TBAF, THF, rt (88%); (f) $CH_2CHC(O)Cl$, DIPEA, CH_2Cl_2, −50 °C (77%); (g) 185 °C, toluene, TEMPO, DIPEA, 24 h (79%); (h) NaH, THF, rt (82%); (i) *n*-BuLi, Bu_3SnH, CuCN, THF, −78 °C, 1 h (80%); (j) Pd_2dba_3, TFP, DIPEA, toluene, 110 °C, 2 h (80%); (k) TFA, CH_2Cl_2, 37% aq CH_2O, $NaCNBH_3$ (81%).

the relative steric energies that were calculated for the different stereoisomers **10a**, **10b**, **10c**, and **10d**: 0.0, 9.9, 3.3, and 14.6 kJ mol^{-1}, respectively.[14]

(13) It is worth noting that it was possible to confirm the correct enantiomeric configuration by refinement of the absolute structure parameter, see: Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-180241. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: int.code +44 (1223) 336-033. E-mail: deposit@ccdc.cam.ac.uk].

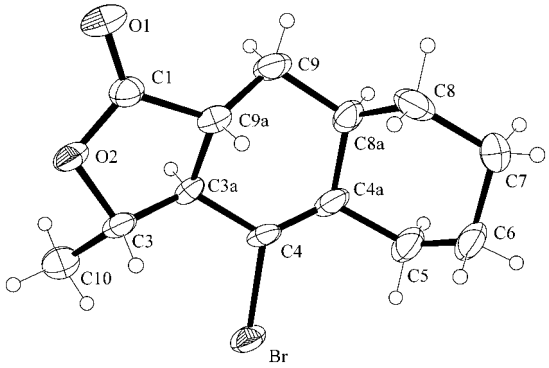
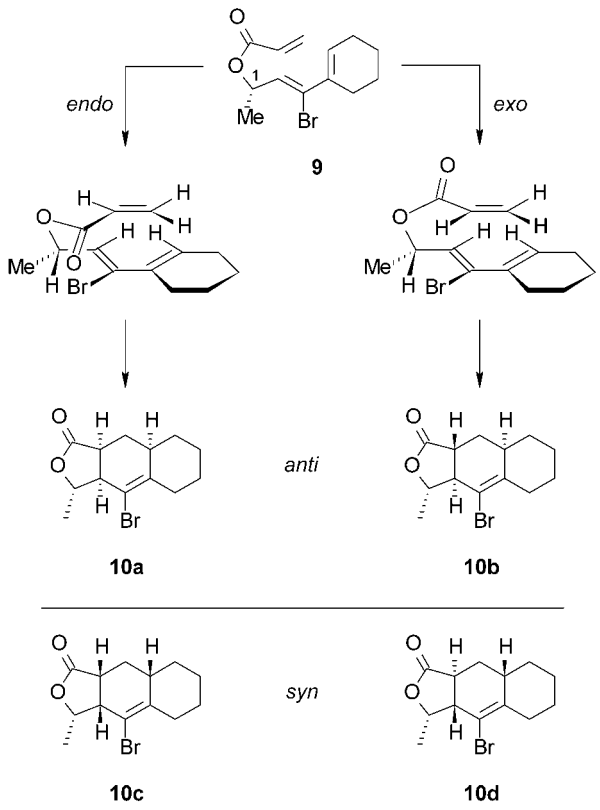


Figure 1. X-ray crystal structure of **10b**.

The stereochemical outcome of the cycloaddition is determined by (1) the *endo* or *exo* mode of addition and (2) the *anti* or *syn* approach of the dienophile relative to the orientation of the methyl group at C-1 (Scheme 3). Steric

Scheme 3



considerations, in particular the interaction of the large Br with the substituents at C-1, are clearly in favor of the *anti* approach shown in the scheme. The preferred *exo* mode (ratio

exo:*endo* = 6.2:1) is in line with previous results that were obtained with several related pentadienyl acrylates.[15] In particular the recent conformational studies of the IMDA reaction of C-1 substituted derivatives by White and Snyder[15b] and Paddon-Row and Sherburn[15c] are enlightening. In these examples the thermal reaction led to the formation of cycloadducts that correspond to the diastereomeric configurations **a**, **b**, and **c** with the preferred formation of *trans*-fused **b** (stereochemical designations as in Scheme 3). It is interesting to note that both groups confirmed the obtained experimental results by combined force field and density functional calculations (Becke3LYP/6-31G(d) level) on model transition structures of their reactions.

The final sequence to **5** first involves a second Stille reaction. Cross-coupling between vinylic bromide **10a** and vinylstannane **8** affords diene **11a** in 80% isolated yield (Pd_2-dba_3, TFP, DIPEA, toluene, reflux, 2 h).[16] After removal of the *N*-Boc protective group (TFA, CH_2Cl_2), the *N*-Me group is introduced via a classical reductive amination (CH_2O, $NaCNBH_3$) to afford **5** in 81% isolated yield.

In conclusion, a short, efficient entry into the ABC-ring skeleton of himbacine-like derivatives has been developed. In its longest linear sequence 7 steps are involved for the synthesis of vinylic bromide intermediates (**10**), which are well suited for the subsequent attachment of the piperidine D-ring via a palladium-catalyzed cross-coupling reaction. The C−C bond construction set involves two Stille couplings and one intramolecular Diels−Alder reaction. The stereochemical outcome of the latter was found to be in accord with recent literature reports. The further potential of the unsaturated bromide **10** in analogue development using cross-coupling reactions will be reported in a full account.

Acknowledgment. G.V.C. thanks the IWT (Instituut voor Wetenschappelijk en Technologisch Onderzoek) for a fellowship.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **6**, **15**, **16**, **9**, **10a**, **10b**, **11a**, and **5** and X-ray crystallographic data for **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Calculated by the MM2* force field implementation of MacroModel, see: MacroModel−An Integrated Software System for Modeling Organic and Bioorganic Molecules using Molecular Mechanics. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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(16) The synthesis of vinylstannane **8** involves the addition of a higher order tributyltin cuprate to the known propargylic amine **17**,[2d] according to (a) Capella, L.; Degl'Innocenti, A.; Mordini, A.; Reginato, G.; Ricci, A.; Seconi, G. *Synthesis* **1991**, 1201. (b) Heutringer, M. H.; Singer, R. D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 9397.