

Natural Products

Total Synthesis of the Biphenyl Alkaloid (–)-Lythranidine**

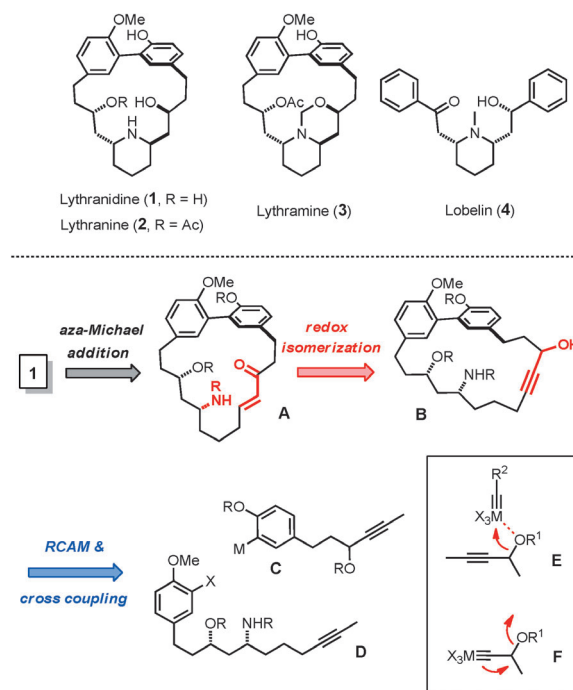
Konrad Gebauer and Alois Fürstner*

Abstract: A sequence comprising a ring-closing alkyne metathesis of a propargyl alcohol derivative, followed by a ruthenium-catalyzed redox isomerization of the derived cycloalkyne and a transannular aza-Michael addition allowed the formation of the distinguishing piperidine-metacyclophane framework of the *Lythraceae* alkaloid lythranidine in a few high-yielding steps. This application attests to the excellent functional-group tolerance of a molybdenum alkylidyne complex endowed with triphenylsilanolate ligands, which enabled the macrocyclization even in the presence of protic functionalities, and thus illustrates the power of contemporary catalytic acetylene chemistry for target-oriented synthesis.

Most alkaloids derived from plants of the *Lythraceae* family comprise a substituted quinolizidine core, however, a small subset features a rather unique piperidine-metacyclophane structure, as illustrated by lythranidine (**1**) and its close relatives lythranine (**2**) and lythramine (**3**; Scheme 1).^[1] Isolated from the perennial plant *Lythrum anceps* Makino,^[2] which serves as herbal remedy as well as for ritual purposes in Japan (“miso-hagi”, “bon-bana”), the 2,6-piperidine-diethanol subunit of **1–3** bears a certain resemblance to *Lobelia* alkaloids such as lobelin (**4**), a well-known respiratory stimulant. The 2,6-*trans*-stereochemistry in **1–3** and the presence of a macrocyclic frame with an embedded biphenyl motif are distinguishing structural elements. The diaryl axis of **1–3** is considerably skewed to relieve unfavorable interactions between the peripheral phenol and phenol ether sites; however, the barrier remains small enough that the rotamers can equilibrate and atropisomers do not persist in solution.^[3]

Although these unusual structural attributes led to fairly detailed physico-chemical studies,^[3,4] preparative approaches to this class of alkaloids and biological studies are scarce. The only known forays to racemic **1** were either completely unselective or even delivered a C3,C11-bis-epimeric product, and therefore hardly meet today’s standards.^[5,6] Encouraged by this state of affairs, we now present the first concise and stereoselective total synthesis of optically pure **1** as the parent compound of this family.

Our synthesis plan centered on the perception that the formation of the 2,6-*trans*-disubstituted piperidine ring might



Scheme 1. Selected *Lythraceae* alkaloids and retrosynthetic analysis of lythranidine (**1**). The inset shows possible decomposition pathways on attempted metathesis of propargylic alcohol derivatives. X = generic anionic ligand.

be linked with the macrocyclization event through catalytic acetylene chemistry (Scheme 1). To this end, a ring-closing alkyne metathesis (RCAM)^[7,8] reaction of a propargylic alcohol derivative was envisaged as the key strategic maneuver. Such substrates however, although potentially highly versatile,^[9] had basically been beyond reach of alkyne metathesis for two major reasons: on the one hand, they are endangered upon contact with the standard alkylidyne catalysts, most of which are fairly Lewis acidic species by virtue of their high-valent d⁰ metal center (compare with the putative adduct of type **E**).^[10] Even if they stay uncompromised and enter into the catalytic cycle in the first place, propargyl alcohol derivatives may not subsist as they can give rise to metal alkylidyne intermediates of type **F**, which carry a potential leaving group next to the nucleophilic carbon center. In fact, it was only recently that we were able to show that such substrates can be successfully engaged with the help of molybdenum alkylidyne complexes endowed with triarylsilanolate ligands as the most active and selective catalysts presently available.^[11,12] Yet, only a small set of model compounds has been investigated so far and the methodology needs further scrutiny by implementation into more demanding settings. The lythranidine case provides an excellent

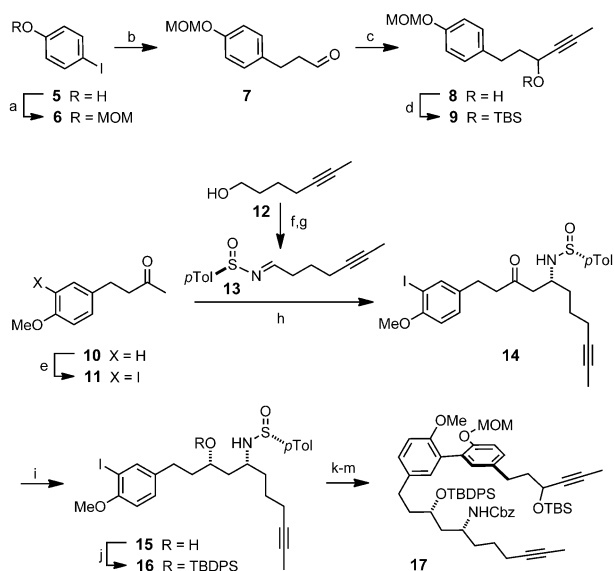
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opportunity: supposed that a macrocyclic compound of type **B** can be formed in this way, a subsequent ruthenium-catalyzed redox isomerization^[13] should unravel an enone **A**, which in turn might intercept a transannular amine donor^[14,15] and hence allow the lythranidine skeleton to be forged in a few straightforward operations.

The necessary building blocks of type **C** and **D** were readily prepared and assembled, as shown in Scheme 2. A



Scheme 2. a) NaH, MOMCl, THF, 0°C→RT, 99%; b) allyl alcohol, Pd(OAc)₂ (1 mol %), Bu₄NCl, NaHCO₃, DMF, 50°C, 80%; c) propynylmagnesium bromide, THF, 0°C→RT, 71%; d) TBSCl, imidazole, DMAP, CH₂Cl₂, 0°C→RT, 98%; e) I₂, Ag₂SO₄, MeOH, 89%; f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78°C→RT, 90%; g) (*R*)-*p*Tol-S(O)NH₂, Ti(OEt)₄, CH₂Cl₂, reflux, 92%; h) KHMDS, Et₂O, -78°C, then **13**, 64% (+ 6% of diastereomer); i) LiAlH(OtBu)₃, LiCl, Et₂O, -78°C, 79% (+ 16% of the 1,3-*anti* isomer); j) TBDPSCl, imidazole, DMAP, CH₂Cl₂, 0°C→RT, 90%; k) (1) **9**, *t*BuLi, Et₂O, 0°C; (2) ZnCl₂, THF; (3) **16**, Pd(PPh₃)₄ (2.5 mol %), THF, 60°C, 75%; l) Dess–Martin periodinane, MeCN/CH₂Cl₂/H₂O (8:8:1), 76%; m) CbzCl, Et₃N, EtOAc, 0°C→RT, 79%; Cbz = benzyloxycarbonyl; DMAP = 4-dimethylaminopyridine; KHMDS = potassium hexamethyldisilazide; MOM = methyloxymethyl; TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; *p*Tol = *p*-tolyl.

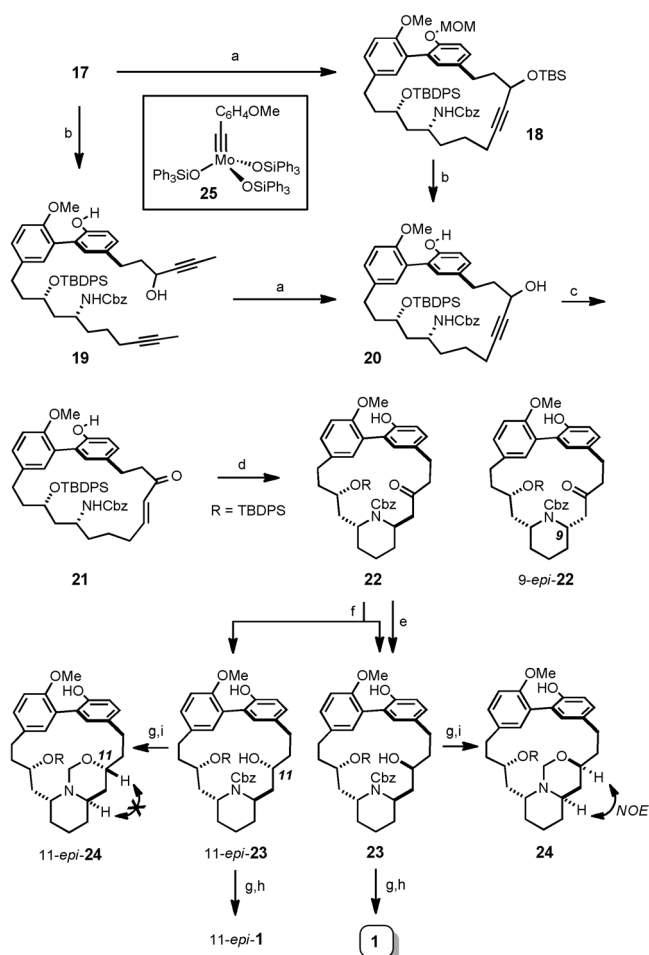
Heck reaction of the MOM-protected 4-iodophenol **6** with allyl alcohol^[16] readily afforded large amounts of the required propanal derivative **7**. Because the projected redox isomerization would planarize the propargylic alcohol center anyway, there was no need to conduct the addition of the alkynyl donor in an asymmetric fashion. Thus, **7** was simply reacted with commercially available propynylmagnesium bromide and the resulting alcohol **8** was protected as the corresponding TBS-ether **9** prior to cross-coupling with the second arene building block **16**. This compound was prepared by a silver-assisted iodination of commercially available **10** in MeOH, furnishing product **11** with excellent selectivity and in high yield.^[17] The formation of the kinetic potassium enolate followed by the addition of sulfinimine **13** (readily formed from **12** and commercially available (*R*)-*p*-toluenesulfin-

amide)^[18,19] at low temperature gave the desired Mannich product **14**, and was well suited for material throughput.^[20] As expected, the reduction of **14** using LiAlH(OtBu)₃ in Et₂O at low temperature furnished the required 1,3-*syn* configured aminoalcohol **15** with decent selectivity (d.r. = 4.5:1).^[21] As the minor *anti* isomer could be separated by flash chromatography, this route was practical and allowed gram amounts of compound **16** to be secured after silylation of the secondary alcohol.

The *ortho*-directing effect exerted by the MOM group served the selective metalation of **9** with *t*BuLi well,^[22] thus setting the basis for an efficient Negishi cross-coupling reaction with iodide **16** to craft the central biaryl axis.^[23] Because our original plan to maintain the *N*-sulfinyl group throughout the synthesis was thwarted by the inability to perform the projected redox isomerization in the presence of this group, the sulfinamide was selectively cleaved with the help of Dess–Martin periodinane^[24] and replaced by a benzyloxycarbonyl moiety to give diyne **17** as an adequate cyclization precursor.

The macrocyclization of diyne **17** through RCAM worked exceedingly well, even at ambient temperature in the presence of the now commercially available complex **25**,^[25] furnishing the desired product **18** in 91% yield on a 1.4 gram scale (Scheme 3). Concomitant cleavage of the TBS ether and the phenolic MOM acetal with dilute HCl in EtOH readily gave the free propargyl alcohol **20** for the envisaged redox isomerization.^[26] From a chemical viewpoint it is noteworthy that the order of events could also be reversed: thus, RCAM was similarly successful with compound **19**, which contains three different protic sites. If one keeps in mind that free alcohols had precluded alkyne metathesis from occurring as long as standard Schrock alkylidyne complexes had to be used as catalysts,^[7] this outcome is deemed quite remarkable. It illustrates a new facet of the excellent functional-group tolerance of molybdenum alkylidynes endowed with silanates as ancillary ligands,^[8,12,25] and augurs well for future applications of this methodology to even more highly decorated substrates.

With the supply of **20** secured, we turned our attention to the formation of the yet missing piperidine ring by a sequence of redox isomerization of the propargylic alcohol followed by transannular aza-Michael addition.^[13,14] To this end, **20** was exposed to catalytic amounts of [IndRu(PPh₃)₂Cl], In(OTf)₃ and camphorsulfonic acid in THF at 80°C. While the desired enone **21** was formed cleanly, a spontaneous heterocycle formation would not proceed under these conditions, as we had originally hoped. Actually, this step turned out to be rather challenging, most likely because of an unfavorable transannular positioning of the reacting sites on the macrocyclic frame of **21**; to complicate matters further, the incipient product **22** is somewhat unstable under harsher conditions. After some optimization, however, the use of *p*TsOH in 1,2-dichloroethane at slightly elevated temperature gave well reproducible results, furnishing the desired piperidine as a mixture of readily separable isomers in favor of the *trans*-disubstituted ring **22** (d.r. = 2.4:1).^[27] Attempts at improving the diastereomeric ratio with the help of chiral Brønsted acids met with no success.



Scheme 3. a) **25** (5 mol %), MS 5 Å, toluene, 91 % (**18**) or 78 % (**20**); b) HCl in EtOH (1 % w/w), 89 % (**20**) or 77 % (**19**); c) [IndRu(PPh₃)₂Cl] (6 mol %), In(OTf)₃ (6 mol %), camphorsulfonic acid (10 mol %), THF, 80 °C, 74 %; d) *p*TsOH (10 mol %), 1,2-dichloroethane, 45 °C, **22** (67 % brsm) + 9-*epi*-**22** (27 % brsm); e) LiAlH(OtBu)₃, LiCl, Et₂O, 0 °C, 92 % (**23**); f) NaBH₄, MeOH, 0 °C, **23** (49 %) + 11-*epi*-**23** (40 %); g) H₂ (1 atm), Pd black (10 mol %), aq. HCl, EtOH, 93 % (65 %, 11-*epi* series); h) TBAF, HOAc, THF, 45 °C, 82 % (**1**); 76 % (11-*epi*-**1**); i) HCHO, MeOH, 76 % (**24**), 61 % (11-*epi*-**24**); brsm = based on recovered starting material; Ind = indenyl; MS = molecular sieves; TBAF = tetra-*n*-butylammonium fluoride; *p*Ts = *p*-toluenesulfonyl.

Gratifyingly though, the reduction of **22** with LiAlH(OtBu)₃ in the presence of excess LiCl was highly selective, although the analysis of the NMR spectra was complicated by the fact that coalescence of the two conformers could not be reached, and the rotamers of the Cbz group further complicate matters. To ensure a definite assignment of the newly formed center, **22** was deliberately subjected to an unselective reduction with NaBH₄. The resulting diastereomers were then transformed into the corresponding *N,O*-acetals **24** and 11-*epi*-**24**, which allowed the configuration of the alcoholic center set through hydride reduction to be assigned by analysis of the NOE contacts and the coupling pattern. However, to this end, the spectra had to be recorded at +90 °C in [D₈]toluene, in which they are not obscured any longer by massive line broadening. After hydrogenolytic cleavage of the Cbz group in **23** in slightly acidic medium, the

spectral fingerprint also became much clearer and allowed the assignments to be confirmed; for details, see the Supporting Information.

The final cleavage^[28] of the TBDPS-ether with TBAF required buffered conditions and proceeded only slowly but gave lythranidine (**1**) in excellent yield and purity. As expected, two equilibrating diastereomers were detected at ambient temperature that relate to the known dynamic of the biaryl motif,^[3,4] reasonably sharp spectra were recorded at +45 °C, which allowed all signals to be resolved and assigned, and hence the constitution and stereostructure of the synthetic samples of **1** to be verified. The diastereomeric product 11-*epi*-**1** was prepared analogously, the spectra of which are distinctly different from those of the natural product.

The route presented herein (15 steps, longest linear sequence, approximately 5 % overall yield) is the first stereoselective entry into a rather intriguing class of alkaloids, which had been known for a long time but went largely untapped by the synthetic community. It attests to the maturity that alkyne metathesis has reached since the advent of new catalysts of largely improved functional-group tolerance.^[8,25] The straightforward and selective formation of a heterocyclic amino-alcohol motif from an acyclic diyne precursor exemplifies that the virtues of this methodology go far beyond the stereoselective formation of olefins by semireduction of the acetylenic products initially formed, which was the most common application in the past.^[29,30] Finally, we would like to emphasize that the present investigation also provides new impetus for the study of transannular reactivity, which had been recognized as inherently powerful early on, but was often difficult to harness in practice.^[15] As the access to macrocyclic rings with well-defined stereochemical patterns becomes increasingly facile, a more systematic survey of this promising reactivity mode seems possible. Ongoing work in this laboratory intends to further illustrate this notion.

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- [1] a) W. M. Gołędebiewski, J. T. Wróbel in *The Alkaloids*, Vol. 18 (Ed.: R. G. A. Rodrigo), Academic Press, New York, **1981**, pp. 263–322; b) K. Fuji in *The Alkaloids*, Vol. 35 (Ed.: B. Arnold), Academic Press, New York, **1989**, pp. 155–176.
- [2] a) E. Fujita, K. Fuji, K. Bessho, A. Sumi, S. Nakamura, *Tetrahedron Lett.* **1967**, 8, 4595–4600; b) E. Fujita, K. Bessho, K. Fuji, A. Sumi, *Chem. Pharm. Bull.* **1970**, 18, 2216–2223; c) E. Fujita, K. Fuji, K. Tanaka, *J. Chem. Soc. C* **1971**, 205–207; d) E. Fujita, K. Fuji, *J. Chem. Soc. C* **1971**, 1651–1653.
- [3] Detailed CD studies showed that the helicity of the biphenyl unit is strongly dependent on the substitution pattern and can be changed by acylation or alkylation of the piperidine *N*-atom and/or the secondary alcohols; the data suggest that **1–3** prefer *M*-helicity in solution, which **2** and a C22-bromo derivative thereof also exhibit in the solid state, see: a) K. Fuji, T. Yamada, E. Fujita, K. Kuriyama, T. Iwata, M. Shiro, H. Nakai, *Chem. Pharm.*

- Bull.* **1984**, 32, 55–62; b) P. J. Cox, G. A. Sim, *Acta Crystallogr. Sect. B* **1982**, 38, 303–306; c) R. J. McClure, G. A. Sim, *J. Chem. Soc. Perkin Trans. 2* **1972**, 2073–2076.
- [4] a) K. Fuji, T. Yamada, E. Fujita, H. Nakai, M. Shiro, *Chem. Pharm. Bull.* **1984**, 32, 63–69; b) K. Fuji, T. Yamada, E. Fujita, *Chem. Pharm. Bull.* **1984**, 32, 70–74.
- [5] K. Fuji, K. Ichikawa, E. Fujita, *Tetrahedron Lett.* **1979**, 20, 361–364.
- [6] W. Carruthers, P. Coggins, J. B. Weston, *J. Chem. Soc. Perkin Trans. 1* **1991**, 611–616.
- [7] a) A. Fürstner, G. Seidel, *Angew. Chem.* **1998**, 110, 1758–1760; *Angew. Chem. Int. Ed.* **1998**, 37, 1734–1736; b) A. Fürstner, O. Guth, A. Rumbo, G. Seidel, *J. Am. Chem. Soc.* **1999**, 121, 11108–11113; c) A. Fürstner, C. Mathes, C. W. Lehmann, *J. Am. Chem. Soc.* **1999**, 121, 9453–9454.
- [8] a) A. Fürstner, *Angew. Chem.* **2013**, 125, 2860–2887; *Angew. Chem. Int. Ed.* **2013**, 52, 2794–2819; b) A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307–2320.
- [9] For a review on the rich chemistry of propargyl alcohols, see: E. B. Bauer, *Synthesis* **2012**, 1131–1151.
- [10] R. R. Schrock, *Chem. Rev.* **2002**, 102, 145–179.
- [11] P. Persich, J. Llaveria, R. Llermet, T. de Haro, R. Stade, A. Kondoh, A. Fürstner, *Chem. Eur. J.* **2013**, 19, 13047–13058.
- [12] For recent applications of RCAM in total synthesis, see: a) C. M. Neuhaus, M. Liniger, M. Stieger, K.-H. Altmann, *Angew. Chem.* **2013**, 125, 5978–5983; *Angew. Chem. Int. Ed.* **2013**, 52, 5866–5870; b) K. Micoine, A. Fürstner, *J. Am. Chem. Soc.* **2010**, 132, 14064–14066; c) V. Hickmann, A. Kondoh, B. Gabor, M. Alcarazo, A. Fürstner, *J. Am. Chem. Soc.* **2011**, 133, 13471–13480; d) K. Lehr, R. Mariz, L. Leseurre, B. Gabor, A. Fürstner, *Angew. Chem.* **2011**, 123, 11575–11579; *Angew. Chem. Int. Ed.* **2011**, 50, 11373–11377; e) W. Chaładaj, M. Corbet, A. Fürstner, *Angew. Chem.* **2012**, 124, 7035–7039; *Angew. Chem. Int. Ed.* **2012**, 51, 6929–6933; f) K. Micoine, P. Persich, J. Llaveria, M.-H. Lam, A. Maderna, F. Loganzo, A. Fürstner, *Chem. Eur. J.* **2013**, 19, 7370–7383; g) J. Willwacher, A. Fürstner, *Angew. Chem.* **2014**, 126, 4301–4305; *Angew. Chem. Int. Ed.* **2014**, 53, 4217–4221.
- [13] a) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **1995**, 117, 9586–9587; b) B. M. Trost, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, 130, 11970–11978.
- [14] For pertinent examples of heterocycle formations by redox isomerization followed by intramolecular 1,4-addition reactions, see: a) B. M. Trost, N. Maulide, R. C. Livingston, *J. Am. Chem. Soc.* **2008**, 130, 16502–16503; b) B. M. Trost, A. C. Gutierrez, R. C. Livingston, *Org. Lett.* **2009**, 11, 2539–2542.
- [15] For general reviews on transannular reactions, see the following and literature cited therein: a) P. A. Clarke, A. T. Reeder, J. Winn, *Synthesis* **2009**, 691–709; b) E. Marsault, A. Toro, P. Deslongchamps, *Tetrahedron* **2001**, 57, 4243–4260; c) D. C. Harrowven, G. Pattenden in *Comprehensive Organic Synthesis*, Vol. 3 (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 379–411.
- [16] L. F. Tietze, K. Kahle, T. Raschke, *Chem. Eur. J.* **2002**, 8, 401–407.
- [17] Likely because of the voluminous AgI precipitate that is formed during the course of the reaction, the nature of the medium plays an important role; in any case, much better results were obtained on larger scale with MeOH rather than EtOH as the solvent, the latter of which had been used previously for similar transformations, see: W.-W. Sy, *Tetrahedron Lett.* **1993**, 34, 6223–6224.
- [18] F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, 64, 1403–1406.
- [19] (*R*)-*tert*-Butylsulfonamide was found less adequate as auxiliary in the present case; the diastereomeric ratio in the Mannich step was marginally better, but selective deprotection at a later stage with Dess–Martin periodinane could not be accomplished. For a review on (*R*)-*t*BuS(O)NH₂, see: M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, 110, 3600–3740.
- [20] F. A. Davis, B. Yang, *Org. Lett.* **2003**, 5, 5011–5014.
- [21] F. A. Davis, P. M. Gaspari, B. M. Nolt, P. Xu, *J. Org. Chem.* **2008**, 73, 9619–9626.
- [22] *Organometallics in Synthesis. A Manual*, 2nd ed. (Ed.: M. Schlosser), Wiley, Chichester, **2002**.
- [23] E. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, 80, 233–257.
- [24] F. A. Davis, T. Ramachandar, H. Liu, *Org. Lett.* **2004**, 6, 3393–3395.
- [25] a) J. Heppekaussen, R. Stade, A. Kondoh, G. Seidel, R. Goddard, A. Fürstner, *Chem. Eur. J.* **2012**, 18, 10281–10299; b) J. Heppekaussen, R. Stade, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2010**, 132, 11045–11057.
- [26] It is pointed out that the redox isomerization did not proceed with the MOM group in place.
- [27] As both isomers were available, the stereochemical assignment is unambiguous and based on NOESY contacts and the *J*-coupling patterns, see the Supporting Information.
- [28] The order of deprotection is important. When the TBDPS group was cleaved prior to Cbz deprotection, a cyclic carbamate was formed that could not be converted into **1**.
- [29] A. Fürstner, *Science* **2013**, 341, 1357 (UNSP 1229713).
- [30] For previous applications of RCAM to the synthesis of structural motifs other than alkenes, see Ref. [11] and the following: a) G. Valot, C. S. Regens, D. P. O'Malley, E. Godineau, H. Takikawa, A. Fürstner, *Angew. Chem.* **2013**, 125, 9713–9717; *Angew. Chem. Int. Ed.* **2013**, 52, 9534–9538; b) S. Benson, M.-P. Collin, A. Arlt, B. Gabor, R. Goddard, A. Fürstner, *Angew. Chem.* **2011**, 123, 8898–8903; *Angew. Chem. Int. Ed.* **2011**, 50, 8739–8744; c) L. Brewitz, J. Llaveria, A. Yada, A. Fürstner, *Chem. Eur. J.* **2013**, 19, 4532–4537; d) A. Fürstner, O. Larionov, S. Flügge, *Angew. Chem.* **2007**, 119, 5641–5644; *Angew. Chem. Int. Ed.* **2007**, 46, 5545–5548; e) A. Fürstner, S. Flügge, O. Larionov, Y. Takahashi, T. Kubota, J. Kobayashi, *Chem. Eur. J.* **2009**, 15, 4011–4029; f) A. Fürstner, A.-S. Castanet, K. Radkowski, C. W. Lehmann, *J. Org. Chem.* **2003**, 68, 1521–1528; g) L. Hoffmeister, P. Persich, A. Fürstner, *Chem. Eur. J.* **2014**, 20, 4396–4402.

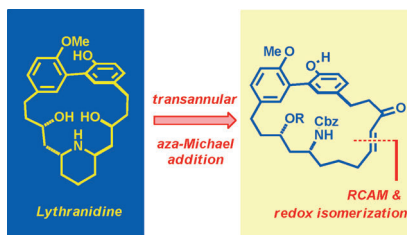
Communications



Natural Products

K. Gebauer, A. Fürstner* — ■■■■-■■■■

Total Synthesis of the Biphenyl Alkaloid
(-)-Lythranidine



Triple: The distinguishing piperidine-metacyclophane framework of the *Lythraceum* alkaloid lythanidine was formed by ring-closing alkyne metathesis (RCAM) of a propargylic alcohol derivative followed by redox isomerization and a proton-catalyzed transannular aza-Michael addition as the key steps. This straightforward approach illustrates the enabling power of catalytic alkyne chemistry for target-oriented synthesis.