Pergamon

Tetrahedron Letters, Vol. 38, No. 19, pp. 3369-3372, 1997
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0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00632-1

Synthetic Studies on the Perhydropyrrolo[2,1-*j*]quinoline Marine Alkaloids Lepadiformine and Cylindricine C Using a 2-Azapentadienyl Anion Cycloaddition. Synthesis of 2,13-Diepilepadiformine (or 2-Epi-11-deoxycylindricine C).

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Abstract: Tin-lithium exchange of **13** with *n*-BuLi produced the 2-azapentadienyl anion **6** (R = CH_3), which participated in a [π4s+π2s] cycloaddition reaction with phenyl vinyl sulfide to afford the spirocyclic pyrrolidine **14**, which as coverted to 2,13-diepilepadiformine (or 2-epi-11-deoxycylindricine C) **17** by a sequence of steps involving oxidative cleavage of the propenyl side-chain, intramolecular reductive amination, and desulfurization.
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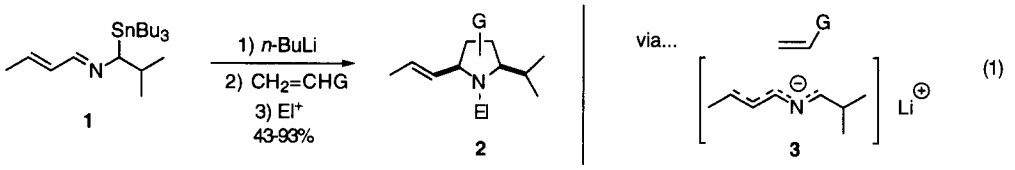
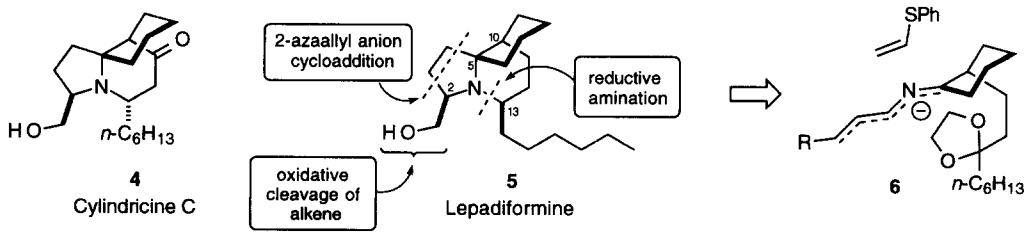
Previous reports from these laboratories have addressed the synthesis of pyrrolidines, 1-pyrrolines, and pyrroles by the [4πs+2πs] cycloaddition of non-stabilized 2-azaallyl anions with alkenes ("anionophiles").[2] In addition, we have reported similar cycloadditions with 2-azapentadienyl anions **3** prepared by tin-lithium exchange of conjugated α'-stannyl imines **1** (eq. 1).[3] The resultant pyrrolidines **2** bear an alkenyl group at C(2), providing an opportunity for further functionalization. Herein we report our initial studies on the use of 2-azapentadienyl anion cycloadditions for the synthesis of pyrrolidine-containing alkaloids. These studies required the development of an alternate 2-azapentadienyl anion precursor.



1 **2** **3**

The cylindricines (e.g., cylindricine C, **4**), discovered by Blackman, *et. al*,[4] and lepadiformine **5**, discovered by Biard, *et. al*[5] are new marine alkaloids isolated recently from the ascidians *Clavelina cylindrica* and *Clavelina lepadiformis*, respectively. The perhydropyrrolo[2,1-*j*]quinoline skeleton represents a new structural class, one that has not yet seen synthetic activity. We chose to embark on a synthesis of lepadiformine **5** using the disconnections shown. The hydroxymethyl side-chain would arise from oxidative

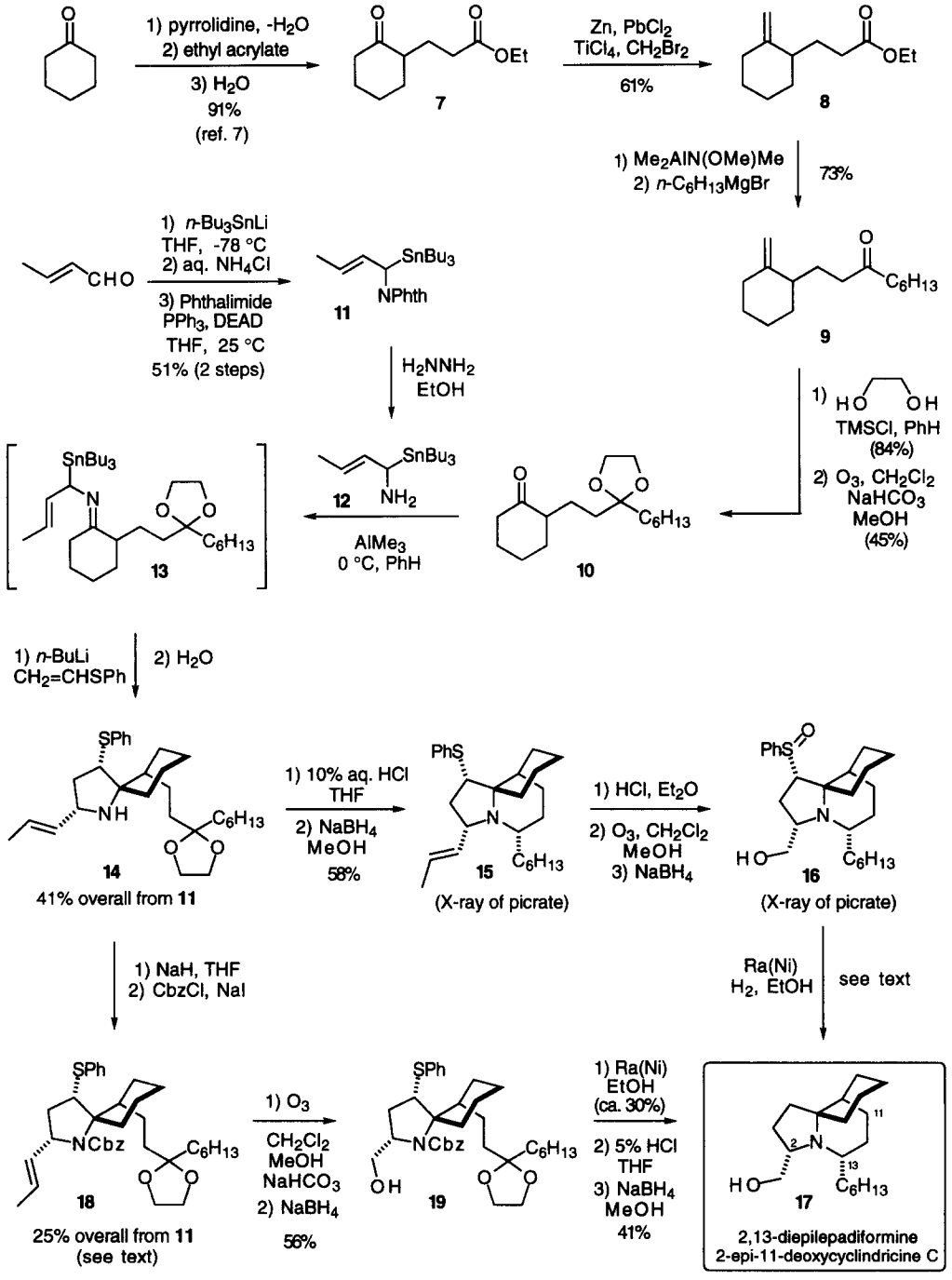


4 Cylindricine C **5** Lepadiformine **6**

cleavage of an alkenylpyrrolidine, which would be assembled using a 2-azapentadienyl anion cycloaddition with phenyl vinyl sulfide, an ethylene equivalent, as shown for **6**. The piperidine ring would be installed by an intramolecular reductive amination. The relative configuration of C(5) and C(10) (Biard's numbering[5]) would result from cycloaddition from the face of the 2-azapentadienyl anion opposite the side-chain of **6**.[6] The relative configuration of C(2) vs. C(5)/C(10) will depend on the geometry of the 2-azapentadienyl anion, about which little is known. However, we felt that we could adjust this configuration by epimerization of a carbonyl compound derived from oxidative cleavage of the alkenyl side chain after cycloaddition. Should C(2) be set correctly, intramolecular reductive amination involving axial attack on an intermediate iminium ion was predicted to occur with the correct relative configuration at C(13). Our initial investigations into the synthesis of this novel ring system, resulting in a synthesis of **17**, a stereoisomer of lepadiformine (also a stereoisomer of 11-deoxycylindricine C), are outlined in Scheme 1.

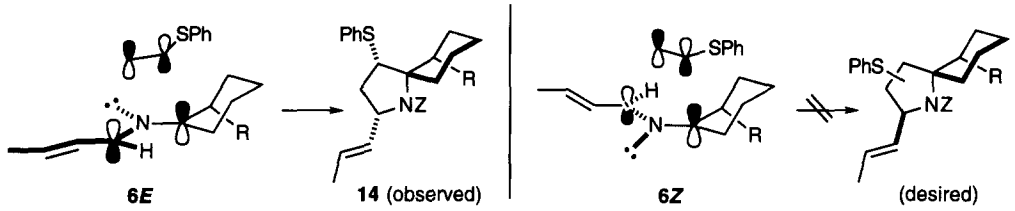
The known ketoester **7**, prepared using Stork's enamine method,[7] was methylenated according to the Takai protocol,[8] affording the ester **8**. Weinreb amide formation and reaction with *n*-hexylmagnesium bromide gave the ketone **9**,[9] which after ketalization and ozonolysis afforded **10**. At this stage, our prior work on the generation of 2-azapentadienyl anions by tin-lithium exchange would require Bu_3SnLi addition to **10** followed by a Gabriel-type synthesis of an amine and subsequent condensation with crotonaldehyde.[2b,3,10] This method is obviously inappropriate in this case, since a Gabriel synthesis on a tertiary α-stannyl alcohol would fail. We therefore examined the stannane **13** as an alternative 2-azapentadienyl anion precursor. Thus, Bu_3SnLi was added to crotonaldehyde and the resultant α-stannyl alcohol was converted to the phthalimide **11** using a Mitsunobu reaction. Hydrazinolysis of **11** gave the amine **12**,[2b,10] which was immediately condensed with the ketone **10** to produce the stannyl imine **13**. Without purification, **13** was mixed with phenyl vinyl sulfide and added to a cold solution of *n*-BuLi. Quenching the cycloaddition reaction with water provided the pyrrolidine **14** as a single stereo- and regioisomer in 41% yield based on the phthalimide **11**. The stereochemical assignment of **14** awaited further transformations. Hydrolysis of the ketal followed by hydride reduction of the intermediate iminium ion gave **15**, the first synthetic compound with the lepadiformine/cylindricine skeleton, again as one stereoisomer. Oxidative cleavage of the propenyl side-chain proved to be problematic, perhaps due to the presence of the amine. After the examination of several oxidative methods, ozonolysis of the hydrochloride salt of **15** followed by workup with $NaBH_4$ was found to afford the sulfoxide **16**. Raney nickel desulfurization of **16** gave a low yield of **17**,[11] which was found to be similar to, but not identical with a sample of lepadiformine kindly provided by Professor J. F. Biard. Suspecting we had made a stereoisomer of lepadiformine, compounds **15** and **16** were converted to their picrate salts and crystallized from CH_2Cl_2/hexane. X-Ray crystallographic determinations of the picrates of **15** and **16** showed that **15** and **16** (and thus **17**) are epimeric with lepadiformine at C(2) and C(13), and epimeric with 11-deoxycylindricine C at C(2). The relative configuration at C(5) and C(10) is correct, validating our model for the facial selectivity of the cycloaddition (see **6**).

An alternate approach to **17** from **14** was examined in an attempt to optimize the oxidative cleavage of the propenyl side-chain. Thus, starting with the phthalimide **11**, hydrazinolysis, condensation with **10**, transmetalation, cycloaddition, aqueous workup, and a relatively difficult installation of a carbobenzyloxy group afforded the carbamate **18** in 25% overall yield. Ozonolysis of **18** followed by a reductive workup gave **19** in reasonable yield, which was subjected to Raney nickel desulfurization and intramolecular reductive amination to afford 1,13-diepilepadiformine (2-epi-11-deoxycylindricine C) **17**.



Scheme 1. Synthesis of the lepadiformine/cylindricine skeleton.

The incorrect configuration at C(2) may result from a cycloaddition involving the all-*E* geometry of the 2-azapentadienyl anion, i.e. **6*E*** shown below, rather than the stereoisomer **6*Z***, which has the *Z*-geometry at the original imine.[12] Once C(2) is set, it may then direct the stereoselectivity of the reductive amination. Should we be able to adjust the configuration at C(2) prior to reductive amination, perhaps by converting it to an aldehyde or ester and epimerizing, or by introducing this substituent on a C(2)-unsubstituted pyrrolidine, the stereoselectivity of the reductive amination may also be altered. Studies along these lines are underway.



Acknowledgement. We thank the National Institutes of Health (GM-52491) for support of this research and for an Individual National Research Service Award (CA-66256) to NSB. We also thank Professors J. F. Biard (Université de Nantes) and A. J. Blackman (University of Tasmania) for helpful correspondence and a sample of authentic lepadiformine (Biard) and spectra of cylindricine C (Blackman).

NOTES AND REFERENCES

(1) Author to whom correspondence regarding the X-ray crystallographic determinations should be directed.

(2) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett* **1988**, *29*, 761-764. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329-1345. (c) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354-6357. (d) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641-2644. (e) Pearson, W. H.; Postich, M. J. *J. Org. Chem* **1994**, *59*, 5662-5671. (f) Pearson, W. H.; Lovering, F. E. *Tetrahedron Lett.* **1994**, *35*, 9173-9176. (g) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336-12337.

(3) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001-7004.

(4) (a) Blackman, A. J.; Li, C.; Hockless, D. C. R.; Skelton, B. W.; White, A. H. *Tetrahedron* **1993**, *49*, 8645-8656. (b) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1994**, *47*, 1355-1361. (c) Li, C.; Blackman, A. J. *Aust. J. Chem.* **1995**, *48*, 955-965.

(5) Biard, J. F.; Guyot, S.; Roussakis, C.; Verbist, J. F.; Vercauteren, J.; Weber, J. F.; Boukef, K. *Tetrahedron Lett.* **1994**, *35*, 2691-2694.

(6) Approach of the alkene from the face of the 2-azapentadienyl anion opposite to the 2-alkyl group is precedented in the diasteroselective alkylation of exocyclic enolates involving 1,2-asymmetric induction, where A(1,3) strain is known to force the 2-alkyl group into the axial position. See: (a) Evans, D. A. In *Asymmetric Synthesis*; J. D. Morrison, Ed.; Academic Press: New York, 1984; Vol. 3; pp 1-110. (b) Krapcho, A. P.; Dundulis, E. A. *J. Org. Chem* **1980**, *45*, 3236-3245.

(7) Stork, G.; Brizzolara, A.; Landesman, J.; Szmuskovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(8) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *27*, 2417. (b) Okazoe, T.; Hibino, J.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5581. (c) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

(9) (a) Nahm, S.; Weinreb, S. M.; *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

(10) Chong, J. M.; Park, S. B. *J. Org. Chem* **1992**, *57*, 2220-2222.

(11) A separate experimental run was performed, starting with the phthalimide **11** and proceeding to **17** without purification of intermediates, resulting in a 1.8% overall yield (unoptimized). The Raney nickel step was estimated to proceed in about 28% yield.

(12) The anions **6*E*** and **6*Z*** are shown as the "W" geometry. The cycloadduct **14** might also also arise from the "U" geometry of **6*Z***, as suggested by a referee. However, at least for 2-azaallyl anions, the "W" form appears to be the most likely. See reference 2c above and the references cited therein.

(*Received in USA* 5 *March* 1997; *revised* 28 *March* 1997; *accepted* 29 *March* 1997)