Ireland-Claisen Rearrangements of Enediyne Lactones: Tandem Claisen-Bergman Strategy for Stereocontrolled Tetrahydronaphthalene Synthesis

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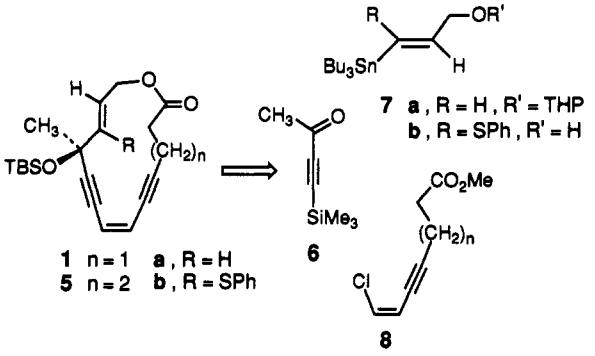
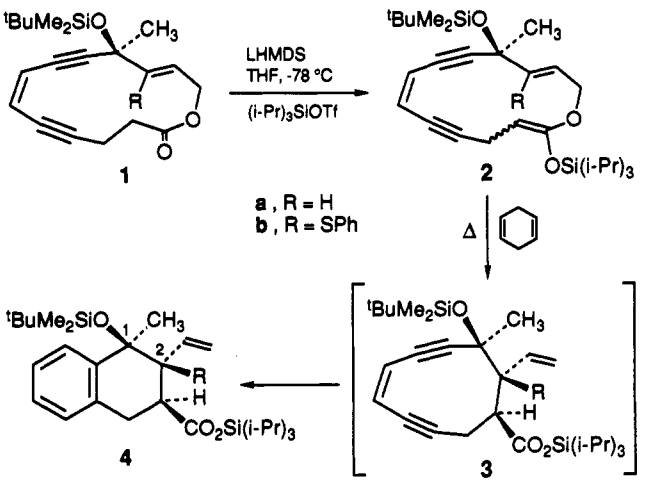
Recent investigations concerning the fascinating biological action of enediyne antibiotics have brought the Bergman rearrangement to the fore as the most important mechanistic event giving rise to DNA-cleaving 1,4-dehydrobenzene intermediates.[1] Conceptually, a chemical activation step leads to a structural change within each antibiotic that accelerates Bergman aromatization.[2] We were intrigued by the prospective synthetic potential of this concept employing a Claisen rearrangement of 14-membered enediyne lactones **1** as both the activation and the stereogenic step.[3] Specifically, Bergman cyclization of 10-membered enediynes **3** triggered by Ireland-Claisen rearrangement[4] of ketene acetals **2** was envisioned to produce tetrahydronaphthalene derivatives **4** from nonaromatic precursors in a stereocontrolled fashion (Scheme I). In this communication we report the *first stereoselective synthetic application involving the Bergman reaction* and several novel stereochemical features of the lactonic Ireland-Claisen rearrangement, results which should have significant importance in the synthesis of biologically active substances.[5]

The synthesis of 15-membered lactones **5** (eq 1) was also targeted in order to probe the Claisen process separately, since the 11-membered enediyne products were expected to be stable to Bergman aromatization.[6] In practice, noteworthy aspects of



the construction of lactones **1b** and **5b** include the use of (*E*)-1-(phenylthio)vinylstannane (**7b**),[7] the compatibility of the phenylthio substituent with Pd(0)-catalyzed couplings of chloroenyne esters **8**[8] with enynol **9** (Chart I),[9] and the efficient

Scheme I



macrolactonization of coupled products (70–80% isolated yields).[10] In turn, enynol **9** was prepared in 50% overall yield by addition of 4-(trimethylsilyl)-3-butyn-2-one (**6**)[11] to the Ce(III) derivative of **7b** (2.0 equiv of *n*-BuLi, 2.1 equiv of anhydrous $CeCl_3$, –60 °C), followed by protective group adjustment.[9d] Phenylthionorlactones **1a** and **5a** were synthesized[12] in a similar manner starting with vinylstannane **7a**.[13]

Considerable experimentation with lactones **5** (eq 1) established the combination of lithium bis(trimethylsilyl)amide (LHMDS) and triisopropylsilyl triflate as an effective protocol for forming and handling the required ketene acetals **10** (Chart I).[14] Under these conditions,[15] the predominance of (*E*)-**10a** (9:1, 80% yield) and (*E*)-**10b** (10:1, 85% yield) was consistent with precedent on lactone enolizations.[3] However, inclusion of HMPA (3.5 equiv) gave rise to (*Z*)-ketene acetals **10a** (10:1, 90% yield) and **10b**

(1) For reviews describing mechanistic and DNA-cleaving studies of calicheamicin/esperamicin and dynemicin, see: (a) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387. (b) Lee, M. D.; Ellestad, G. A.; Borders, D. B. *Acc. Chem. Res.* **1991**, *24*, 235.

(2) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. (b) Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. (c) Bharucha, K. N.; Marsh, R. M.; Minto, R. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 3120.

(3) For recent reviews of the Claisen rearrangement, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Blechert, S. *Synthesis* **1989**, *71*. (c) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2. For key papers on the lactonic variation of the Ireland process, see: (d) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (e) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. (f) Cameron, A. G.; Knight, D. W. *Tetrahedron Lett.* **1982**, *23*, 5455. (g) Brunner, R. K.; Borschberg, H.-J. *Helv. Chim. Acta* **1983**, *66*, 2608.

(4) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650. (b) Ireland, R. E.; Wipf, P.; Xiang, J.-N. *J. Org. Chem.* **1991**, *56*, 3572.

(5) For example, tetrahydronaphthalenes such as podophyllotoxin and the clinically prescribed antitumor agent etoposide (Stähelin, H.; von Wartburg, A. *Cancer Res.* **1991**, *51*, 5) could be rapidly constructed using this strategy. For a synthetic application of a Bergman-type diyl as precursor for radical cyclizations, see: Grissom, J. W.; Calkins, T. L. *Tetrahedron Lett.* **1992**, *33*, 2315.

(6) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.

(7) Magriotis, P. A.; Brown, J. T.; Scott, M. E. *Tetrahedron Lett.* **1991**, *32*, 5047. The thiophenyl substituent was selected to serve as a handle in a projected [2,3] allyl sulfoxide–sulfenate rearrangement for the installation of a calicheamicin-type exocyclic double bond in a stable form of enediyne **3** (mono-$Co_2(CO)_6$-complex).

(8) (a) Cologne, J.; Gelin, R. *Bull. Soc. Chim. Fr.* **1954**, 797. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

(9) Couplings succeed (70–75% yields) despite prejudice that sulfur compounds are catalyst poisons. For related observations, see ref 7 and: (a) Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902. (b) Magriotis, P. A.; Scott, M. E.; Kim, K. D. *Tetrahedron Lett.* **1991**, *32*, 6085. (c) Trost, B. M.; Matelich, M. C. *J. Am. Chem. Soc.* **1991**, *113*, 9007. (d) Magriotis, P. A.; Doyle, T. J.; Kim, K. D. *Tetrahedron Lett.* **1990**, *31*, 2541. (e) Hoshino, Y.; Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 3983.

(10) The reagent combination DCC (4.0 equiv)–pyridine (6.0 equiv)–PPTS (4.0 equiv) in $CHCl_3$ at 23 °C was employed, see: (a) Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7407. (b) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(11) (a) Fleming, I.; Perry, D. A. *Tetrahedron* **1981**, *37*, 4027. (b) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786.

(12) Satisfactory NMR (^1H, ^{13}C, and 2D COSY), IR, and/or MS data were obtained for new compounds described herein. Ultimate proof of macrolactone structure was obtained by X-ray analysis of desilylated **5b**.

(13) (a) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265. (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(14) Silylation (TBS-OTf or TIPS-OTf) or methylation (CH_3I) of LDA-derived enolates failed to provide even a trace of silyl ketene acetals or α-methyl lactones, presumably due to "back firing" of protons from diisopropylamine to enolates within relatively stable postenolization complexes (lactones **5** were recovered). For this internal proton return process, see: (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references therein. See also: (b) Damon, D. B.; Hoover, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 6439. (c) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483.

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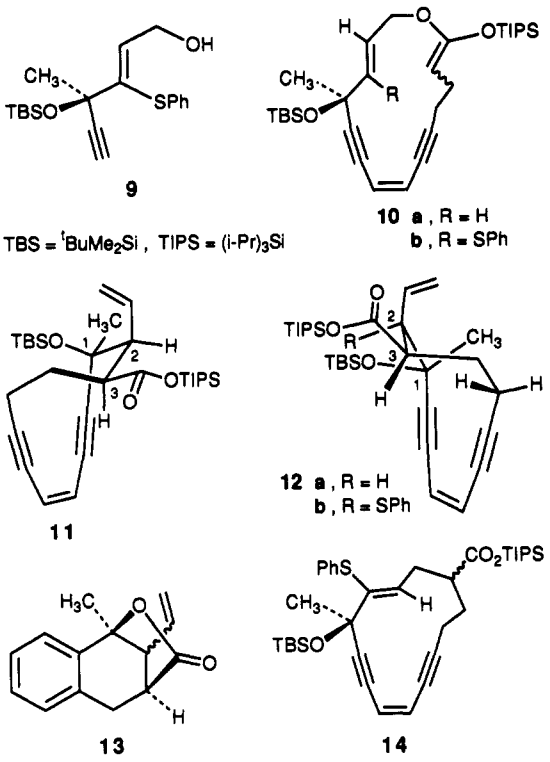
Chart I



(>12:1, 95% yield) *almost exclusively*.[16] To our knowledge, such *efficient control of ketene acetal geometry in macrolactones* comparable to that reported for esters is unprecedented.[3,4] Heating a dilute solution of (*E*)-**10a** in toluene (0.05 M; 110 °C, 2 h) afforded 11-membered enediynes **11** and **12a** in a 3:1 ratio (65% isolated yield), whereas identical treatment of (*Z*)-**10a** led to **12a** and **11** in a 4:1 ratio (75% isolated yield).[17] Since the major products of each reaction, i.e., **11** from (*E*)-**10a** and **12a** from (*Z*)-**10a**, possess the same relative configuration at C-2 and C-3 and yet they are produced from Ireland–Claisen substrates of opposite geometry at the ketene acetal double bond, they must be derived through chairlike (for (*E*)-**10a** → **11**) and boatlike (for (*Z*)-**10a** → **12a**) transition states, respectively. The allylic asymmetric induction observed is noteworthy (>50% de, vide infra).

When a 0.01 M benzene solution of 14-membered ketene acetal (*E*)-**2a**, prepared without HMPA (*E*:*Z* ~ 3:1), was heated at 140 °C (sealed tube) for 5 h in the presence of 1,4-cyclohexadiene (40.0 equiv), an inseparable mixture of tetrahydronaphthalene **4a** and its epimer at C-2 (3:1 ratio) was obtained in 50% yield from **1a** (Scheme I). Relative stereochemistry was determined by desilylation (TBAF, THF, 23 °C) and treatment with MeOH-DCC-DMAP in CH_2Cl_2 at 23 °C in that no *trans*-hydroxy methyl esters were detected, and the resulting two diastereomeric lactones **13** (65% yield from crude **4a**) were conveniently separated (vinyl α:β ~ 3:1).[12] Examination of molecular models indicates that the preferred boatlike transition state is less strained. The viability of the Claisen–Bergman sequence was further demonstrated by conversion (140 °C, 2 h) of ketene acetal **2b** (E:Z ~ 9:1) to tetrahydronaphthalene **4b** (7:1 diastereomeric ratio at C-1)[17a] in 45% yield from **1b**.[12] The high relative asymmetric induction (>75% de) may be attributed to the *antiperiplanar effect* requiring that the allylic C–O bond be nearly perpendicular to the vinyl sulfide plane and anti to the incipient C–C bond in the above transition states.[18]

Unexpectedly, thermolysis of (*E*)- or (*Z*)-**10b** at 110 °C for 16 h produced 13-membered enediynes **14** (2:1 diastereomeric ratio) in 66% isolated yield[12] via a rare [1,3] sigmatropic rearrangement.[3d,19] Apparently, transannular interactions raise prohibitively the energy of both boatlike [3,3] transition states, chairlike ones being inaccessible due to severe pseudo-1,3-diaxial interactions between PhS and OTIPS substituents. A model study, designed to address potential isolation of enediyne **3** as its $Co_2(CO)_6$-η^2-complex,[7] furnished an unprecedented solution to the general problem of controlling [3,3] vs [1,3] sigmatropic reactivity.[20] Thus, the $Co_2(CO)_6$-less hindered acetylene adduct of ketene acetal (*Z*)-**10b** (1.2 equiv of $Co_2(CO)_8$, hexane)[21] underwent in situ Claisen rearrangement at *ambient temperature* (20 h), providing, after oxidative decomplexation (NMNO, hexane, 23 °C), 11-membered enediyne **12b** as a *single isomer* in 70% isolated yield.[17b] The complete stereocontrol induced by allylic asymmetry at lower temperature is notable (cf. (*Z*)-**10a** → **12a**) and, together with the novel conformational mode of controlling reactivity, may prove to be a useful tool in organic synthesis design.

In summary, the combination of an Ireland–Claisen rearrangement and a Bergman aromatization of enediyne substrates provides a rapid, stereocontrolled route to useful tetrahydronaphthalenes from nonbenzenoid precursors.[5,22] The demonstrated availability of 11-membered enediynes such as **11** and **12** paves the way for extension of this strategy to include the Myers aromatization[23] toward a stereoselective construction of 7-membered and possibly 8- and 9-membered benzannulated ring systems.

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Supplementary Material Available: Spectral data for **1, 2, 4, 5, 9-14** and synthetic intermediates toward lactones **1** and **5**; reproductions of selected 2D NOESY spectra; MM2 minimized structure of **12b**; and an ORTEP figure of the X-ray structure of desilylated **5b** (23 pages). Ordering information is given on any current masthead page.

(15) LHMDS, THF, −78 °C, <0.5 min; TIPS-OTf, −78 → 23 °C, 15 min. A small amount of α-TIPS lactone (~10%) was also formed. For α-silylation of carbonyl compounds, see: Larson, G. L. *Pure Appl. Chem.* **1990**, *62*, 2021.

(16) Ketene acetal geometries and ratios were assigned by 2D NOESY experiments and ^{1}H NMR integration of appropriate vinyl hydrogens, respectively. Ketene acetal yields refer to isolated material after nonaqueous workup and rapid chromatographic purification.

(17) (a) Diastereomeric ratios were determined by HPLC analysis. (b) Stereostructures were assigned on the basis of 2D COSY and NOESY data as well as fits of relevant coupling constants to conformations of **11** and **12** having all but two carbons (e.g., C-2 and C-3 of **11**) in a planar arrangement consistent with a reported X-ray analysis of the parent hydrocarbon[6] and the most stable conformation of **12b** calculated by molecular mechanics (see supplementary material).

(18) (a) Caramella, P.; Ronda, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. Apart from its utility in hydroborations, osmylations, and cycloadditions,[22c] this stereoelectronic effect has been pointed out in connection with an ester Ireland–Claisen process: (b) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263. A steric contribution to asymmetric induction cannot be ruled out at this time.

(19) (a) Grieco, P. A.; Clark, J. D.; Jagoe, C. T. *J. Am. Chem. Soc.* **1991**, *113*, 5488 and references therein. (b) Khan, K. M.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1991**, 1699.

(20) For the use of Pd(0) catalyst to reorder [3,3] Caroll-type to [1,3] sigmatropic reactivity, see: (a) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559. For complete diversion of [3,3] Claisen to [1,3] rearrangement in 3.0 M $LiClO_4$–Et_2O, see ref 19a. However, (*E*)- or (*Z*)-**10b** did not undergo [1,3] sigmatropy upon exposure to these conditions.

(21) For precedent on selective complexation of enediynes, see: Magnus, P.; Carter, P.; Elliott, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E. Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544 and earlier work.

(22) The Diels–Alder reaction of benzocyclobutene-derived *o*-quinone methides (*o*-xylylenes) provides tetrahydronaphthalenes from benzenoid starting materials. For selected examples, see: (a) Funk, R. L.; Volhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (b) Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6885. (c) Franck, R. W.; John, T. V.; Olejniczak, K. *J. Am. Chem. Soc.* **1982**, *104*, 1106.

(23) (a) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057. (b) Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130.