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A Tandem 1,3-H-Shift–6π-Electrocyclization–Cyclic 2-Amido-diene Intramolecular Diels–Alder Cycloaddition Approach to BCD-Ring of Atropurpuran

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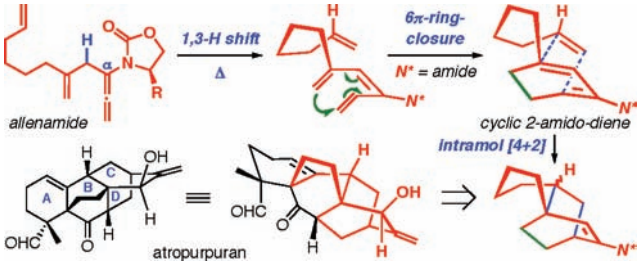
ABSTRACT



An approach toward the BCD-ring of atropurpuran via a sequence of allenic 1,3-H shift, 6π-electron pericyclic ring closure, and intramolecular Diels–Alder cycloaddition of cyclic 2-amidodiene is described.

We recently[1] reported a highly stereoselective tandem sequence consisting of an allenic 1,3-hydrogen shift,[2] a 6π-electron pericyclic ring closure,[3] and an intramolecular Diels–Alder cycloaddition. This three-bond formation cascade provides a facile transformation of simple allenamide **1**[4,5] into the bridged tricycle **4** with four new stereocenters through the intermediacy of 1,3,5-hexatriene **2** and the rare chiral cyclic 2-amido-diene **3**[6–9] [Scheme 1]. While both the hexatriene **2** and the cyclic diene **3**[6] are stable entities that could be intercepted and serve for the ensuing purpose, the entire sequence could proceed in tandem commencing with α-allylated allenamide **1**. In addition, depending upon the substitution pattern of the hexatriene **2** [X = H or halogen], its pericyclic ring closure could be rendered in a diastereoselective manner,[10] thereby constituting a rather impressive long-range 1,6-induction,[11] while setting up a stereochemically regulated intramolecular Diels–Alder cycloaddition [albeit **3a** and **3b** would

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(3) For reviews, see: (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. (b) Okamura, W. H.; de Lera, A. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: New York, 1991; Vol. 5, pp 699–750.

(4) For a leading review on allenamide chemistry, see: Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773.

(5) For general reviews on allenes, see: (a) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004; Vol 1 and 2.

(6) (a) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (b) Hayashi, R.; Feltenberger, J. B.; Lohse, A. G.; Walton, M. C.; Hsung, R. P. *Beil. J. Org Chem.* **2011**, *7*, 410.

(7) For reviews on chemistry of dienamides, see: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Petrzilka, M. *Synthesis* **1981**, 753. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421. (d) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582. (e) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023.

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(9) For some examples cyclic amido-dienes, see: (a) Martínez, R.; Jiménez-Vázquez, H. A.; Delgado, F.; Tamariz, J. *Tetrahedron* **2003**, *59*, 481. (b) Wallace, D. J.; Klauber, D. J.; Chen, C. Y.; Volante, R. P. *Org. Chem.* **2003**, *5*, 4749. (c) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484.

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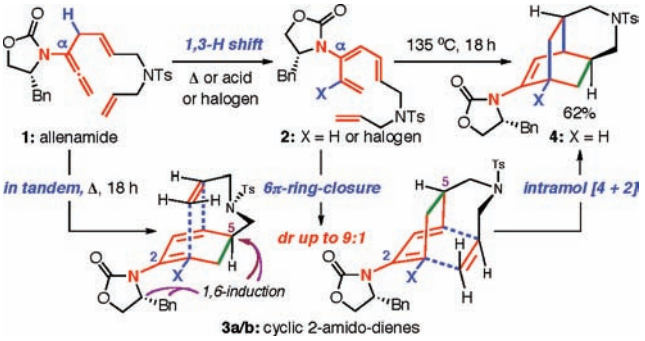
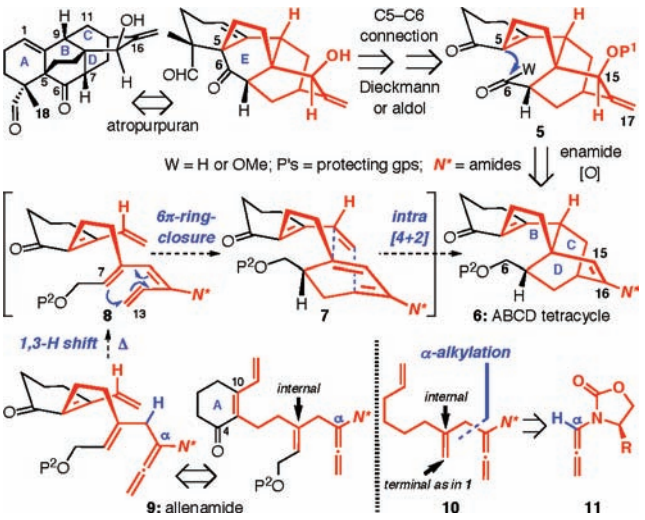
Scheme 1. A Stereoselective Three-Bond Formation Cascade



converge to the same cycloadduct **4**]. We have since been developing a potential application of this methodology to demonstrate its power as this tandem cascade. We wish to communicate here the possibility of employing this tandem sequence as an approach toward the BCD-ring of atropurpuran.

Scheme 2. An Approach to the BCD-Ring of Atropurpuran

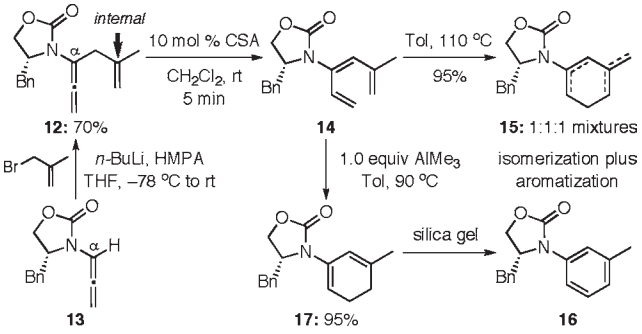


Wang et al. reported the isolation of diterpene atropurpuran [Scheme 2] from *Aconitum hemsleyanum var. atropurpureum*, unveiling an unusual pentacyclic motif containing two contiguous bicyclo[2.2.2]octanes.[12] Although atropurpuran represents the latest example of a unique and brilliant structural topology that *Aconitum genus* has engineered, examples of diterpenes are rare. Most of them are C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids and possess a superb array of medicinal properties.[13] Very recently, Kobayashi[14] reported an elegant approach to the pentacyclic core of atropurpuran.

We have been drawn to the synthesis of the BCD-ring of atropurpuran with the intent to feature our chemistry. As shown in Scheme 2, our tandem sequence could allow transformation of allenamide **9**, a significantly simplified retron, to the ABCD-tetracycle **6** in one operation. The ensuing steps leading to **5** would involve enamide oxidation chemistry that was developed in our group,[15–18] and the final E-ring formation could be envisioned through the formation of C5–C6 bonds. While we are poised with a plan and have elected allenamide **10** to demonstrate the proof-of-concept, the challenge would be that, unlike in allenamide **1**, the dienophile for the Diels–Alder cycloaddition in allenamide **10** [or **9**] is tethered in the *internal* olefinic position of the α-allyl group.

More specifically, we had found that when using an allenamide such as **12** [prepared from **13**[19,20]] substituted at the *internal* olefinic position of the α-allyl group [Scheme 3], the ring-closure step from the triene **14** is problematic, and the resulting cyclic amido diene tends to isomerize and is also prone to oxidation, leading to a mixture of dienes **15** along with arene **16**. The usage of 1.0 equiv of $AlMe_3$ proved to be useful in lowering the thermal activation barrier of the ring closure,[10,21] allowing a more clean isolation of the desired cyclic 2-amido diene **17**. Nevertheless, air oxidation and aromatization of **17** remained a problem.

Scheme 3. Potential Impediment of an Internal Tethering



(11) For some examples of 1,6-remote asymmetric inductions, see: (a) Paterson, I.; Dlgado, O.; Florence, G. J.; Lyothier, I.; Scott., J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35. (b) Arai, Y.; Ueda, K.; Xie, J.; Masaki, Y. *Synlett* **2001**, 529.

(12) Tang, P.; Chen, Q.-H.; Wang, F.-P. *Tetrahedron Lett.* **2009**, *50*, 460.

(13) For recent reviews, see: (a) Wang, F.-P.; Liang, X.-T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2002; Vol. 59, pp 1–280. (b) Atta-ur-Rahman; Choudhary, M. I. Diterpenoid and Steroidal Alkaloids. *Nat. Prod. Rep.* **1999**, *16*, 619. *Nat. Prod. Rep.* **1997**, *14*, 191. *Nat. Prod. Rep.* **1995**, *12*, 361. (c) Yunuzov, M. S. Diterpenoid Alkaloids. *Nat. Prod. Rep.* **1993**, *10*, 471.

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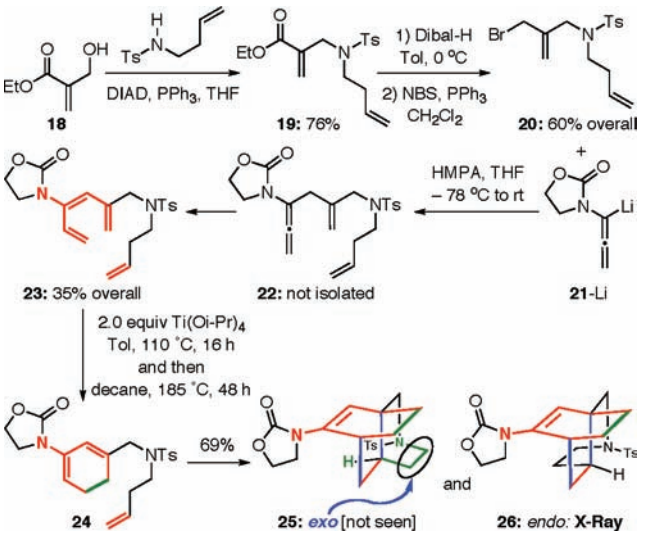
(16) Also see: (a) Adam, W.; Bosio, S. G.; Wolff, B. T. *Org. Lett.* **2003**, *5*, 819. (b) Sivaguru, J.; Saito, H.; Poon, T.; Omonuwa, T.; Franz, R.; Jockusch, S.; Hooper, C.; Inoue, Y.; Adam, W.; Turro, N. J. *Org. Lett.* **2005**, *7*, 2089. (c) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855.

(17) For a leading review on enamide chemistry, see: Carbery, D. R. *Org. Biomol. Chem.* **2008**, *9*, 3455.

(18) Also see: (a) Rappoport, Z. *The Chemistry of Enamines in The Chemistry of Functional Groups*; John Wiley and Sons: New York, 1994. (b) Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517. (c) Hickmott, P. W. *Tetrahedron* 1982, *38*, 1975 and 3363.

(19) See Supporting Information.

Scheme 4. A Successful Sequence with an Internal *N*-Tethering



Intending to investigate these potential problems further, we proceeded to prepare achiral allenamide **22** from ester **18**[22] with nitrogen tethering at the *internal* olefinic carbon. We found that a 1,3-H shift is actually very fast and had occurred during the allylation stage, thereby yielding the triene **23** directly from **21**-Li [Scheme 4]. The ring closure of **23** proved to be challenging, as we initially failed when using high temperature conditions in toluene, xylene, or decane, or employing 1.0 equiv of $AlMe_3$. Only after switching the Lewis acid to Ti(O-*i*-Pr)$_4$ in 2 equiv, we were able to effectively carry out the ring closure in tandem with an intramolecular Diels–Alder cycloaddition, leading to the *endo* cycloadduct **26** as the only isomer. The relative position of the CH_2–NTs fragment defines the *endo* and *exo* sense.

The relative stereochemistry of **26** was unambiguously assigned using the X-ray structure of a single crystal [Figure 1]. It is noteworthy that it would appear that the proposed transition states for both *exo*-**25** and *endo*-**26** are equally feasible, but only the *endo* product was isolated. In addition, we were intrigued by, based on the proposed *endo*-TS, whether long-range stereochemical induction could be again observed here when using chiral amides as shown in cyclic 2-amido diene **27a** [see inside the box of Figure 1]. However, we also recognize that **27** could exist as two possible C–N rotameric conformations **a** and **b**, which could impede or work unfavorably for such a stereoinduction.

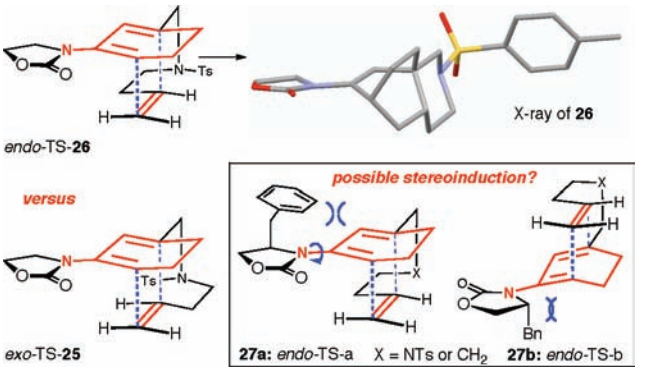
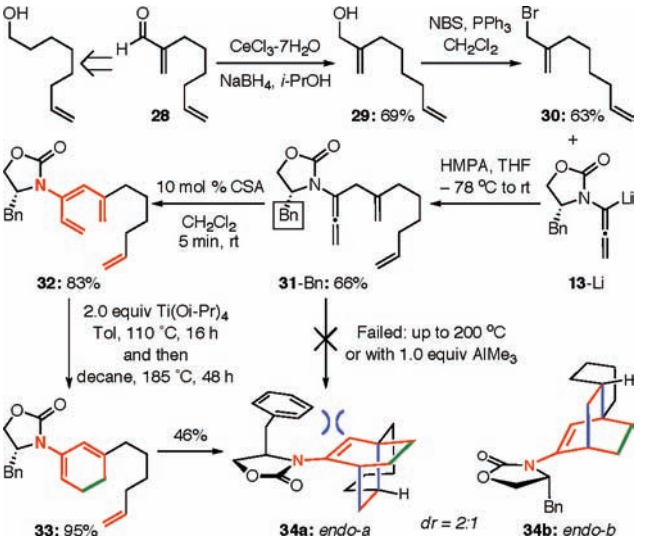


Figure 1. X-ray structure of **26** and proposed *endo*-TS.

Scheme 5. Success in an All-Carbon Internal Tethering



Consequently, we turned our attention to chiral allenamide **31**-Bn, which was synthesized from enal **28**[23] [Scheme 5]. It was quickly evident that each of these *internally* tethered systems behaves quite differently. Initial attempts to directly take **31** to tricycle **34** completely failed under thermal conditions including the use of $AlMe_3$. We then isomerized **31** to triene **32** using 10 mol % CSA and found that, with the use of 1.0 equiv of $AlMe_3$, **32** underwent almost quantitative ring closure to give cyclic 2-amidodiene **33**. However, the intramolecular Diels–Alder cycloaddition proved to be problematic here.[24] To effectively achieve the synthesis of tricycle **34**, the ultimate conditions would involve those adopted in Scheme 4. Tricycle **34** was attained in 46% yield as a mixture of two diastereomers, which would be the two possible *endo*-isomers. The modest ratio implies that achieving a long-range stereochemical

(20) For α-alkylation of allenamides, see: Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

(21) For recent examples using a Lewis acid to mediate 6-π-electron electrocyclic ring closures of 1,3,5-hexatrienes, see: (a) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. C. *Org. Lett.* **2004**, *6*, 3373. (b) Bishop, L. M.; Barbarow, J. E.; Bergmen, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100.

(22) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413.

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(24) IMDA of cyclic 2-amidodiene **33** failed even at 200 °C and with 1.0 equiv of $AlMe_3$. When we attempted 10 mol % Rh(PPh$_3$)$_3$Cl and/or with $AgSbF_6$ at 110 °C, these conditions were also not useful.

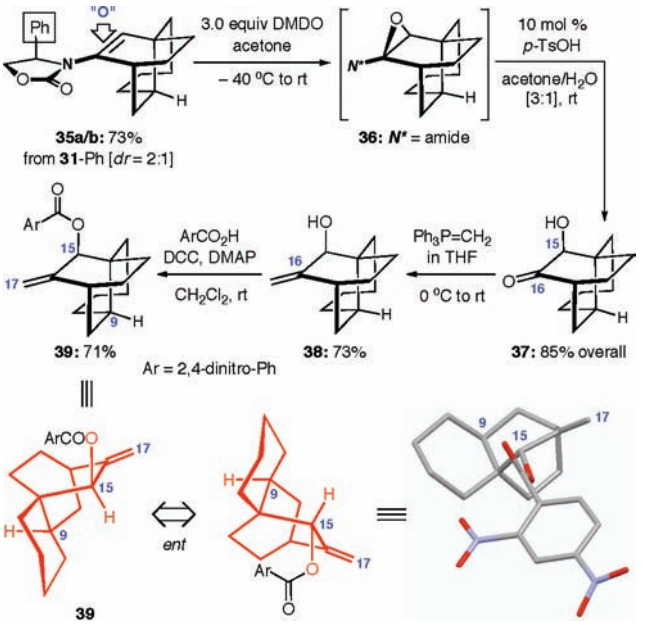
induction is more challenging here based on the TS in Figure 1, or the two competing conformational positions of the amido group [see **27a** versus **27b**] preclude the possibility of having a favorable facial differentiation, although the specifics will await future suitable computational analysis.

Changing the Bn substituent on the Evans auxiliary in **31**-Bn to a Ph group did not improve the diastereoselectivity but gave the respective tricycle **35a/b** in a significantly better overall yield [Scheme 6]. To both demonstrate the enamide oxidation chemistry and concisely assign the relative stereochemistry, we elected to epoxidize **35a/b** as a 2:1 isomeric mixture, and subsequent hydrolysis of the epoxy intermediate **36** unveiled hydroxy ketone **37** as a single diastereomer in 85% yield over two steps. The fact that **37** is a single isomer further suggests that the 2:1 ratio represents the ratio of the two *endo* isomers and not that of *endo*/*exo*. It is also noteworthy that the DMDO epoxidation of **35a/b** was completely stereoselective in favoring the more accessible face of the tricyclic manifold. It is not clear at this point whether the chiral auxiliary plays a cooperative role in the selectivity of the oxidation.

The ensuing Wittig olefination of the C16-carbonyl in **37** afforded allyl alcohol **38** in 73% yield. Preparation of the 2,4-dinitrobenzoyl ester derivative **39** from **38** as well as attaining its X-ray structure allowed us to unambiguously assign the complete carbon skeleton of **38**, which would match that of the BCD-ring of atropurpuran. Given the *endo* nature of the intramolecular Diels–Alder cycloaddition, it appears that to complete a synthesis of atropurpuran, a key epimerization at C9 would be required, which represents an achievable operation based on our actual synthetic plan.

We have described here the feasibility of a synthetic approach toward the BCD-ring of atropurpuran via a sequence of allenic 1,3-H shift, 6π-electron pericyclic ring closure, and intramolecular Diels–Alder cycloaddition of cyclic 2-amidodiene. While the pericyclic ring closure

Scheme 6. X-ray Confirmation and Enamide Oxidation



required the assistance of a Lewis acid, the entire process is highly stereoselective in favor of the *endo*-cycloadduct. Total synthesis efforts toward atropurpuran and a mechanistic understanding of the overall stereoinduction in this process are currently underway.

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Supporting Information Available. Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files. This material is available free of charge via the Internet at http://pubs.acs.org.