ORGANIC LETTERS

2010
Vol. 12, No. 6
1152−1155

Torquoselective Ring Closures of Chiral Amido Trienes Derived from Allenamides. A Tandem Allene Isomerization−Pericyclic Ring-Closure−Intramolecular Diels−Alder Cycloaddition

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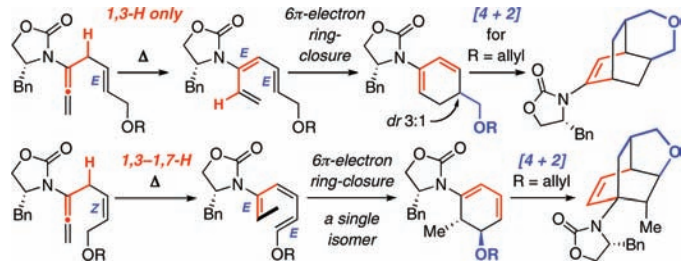
Received December 7, 2009

ABSTRACT



A new torquoselective ring-closure of chiral amide-substituted 1,3,5-hexatrienes and its application in tandem with [4 + 2] cycloaddition are described. The trienes were derived via either a 1,3-H or 1,3-H−1,7-H shift of α-substituted allenamides, and the entire sequence through the [4 + 2] cycloaddition could be in tandem from allenamides.

We recently reported isomerizations of α-substituted allenamides **1** to give amido dienes **2** via stereoselective 1,3-H shift (Scheme 1).[1] In addition, with R = vinyl, the resulting 1,3,5-hexatrienes **2′** were found to be well suited for a 6π-electron electrocyclic ring closure that could be in tandem with the 1,3-H shift, leading to novel chiral cyclic amido dienes **3**[2,3] directly from allenamides.[4,5] The rapid access of 1,3,5-hexatrienes via a simple isomerization of allenes[6–8] allowed us to envision a new torquoselective ring-closure[9–13] involving chiral amido trienes **4**. This asymmetric transformation could potentially lead to a remote 1,6-stereochemical induction while affording cyclic amido dienes **5**, which should be useful for cycloadditions. We communicate here this torquoselective process and its application in tandem with [4 + 2] cycloadditions.

(1) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125.

(2) 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. Also see: (d) Krohn, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1582. (e) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023.

(3) (a) For a review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag: Stuttgart, 2005; Chapter 21.4. (b) For a leading review on recent chemistry of enamides, see: Carbery, D. R. *Org. Biomol. Chem.* **2008**, *9*, 3455. (c) Rappoport, Z. *The Chemistry of Enamines in The Chemistry of Functional Groups*; John Wiley and Sons: New York, 1994.

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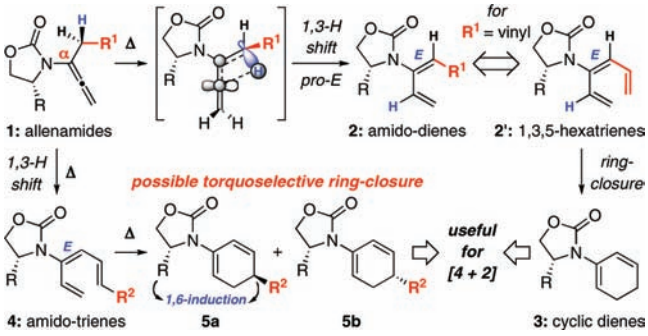
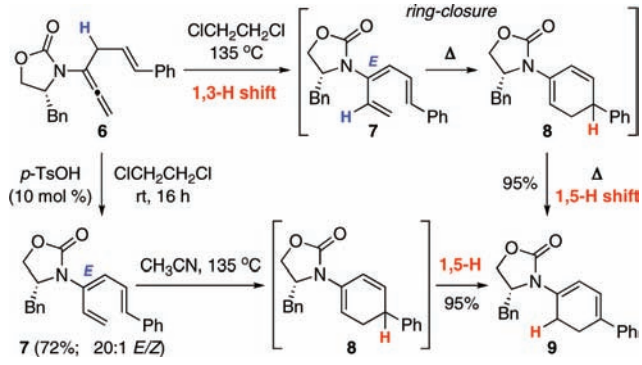
10.1021/ol902821w
Published on Web 02/19/2010

Scheme 1. New Torquoselective Pericyclic Ring Closure



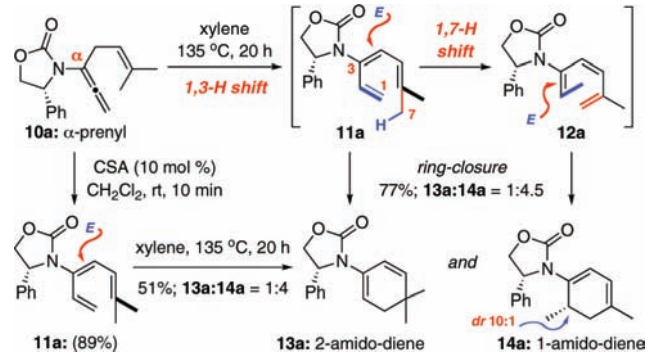
Our intention was quickly met with two unexpected findings. Initially, when heating allenamide **6**[14,15] in $ClCH_2CH_2Cl$ at 135 °C, instead of isolating the desired amido diene **8** from ring closure of the triene **7**, we found **9**[16] in almost quantitative yield, thereby implying a 1,5-H shift had taken place (Scheme 2). Similar results were attained when using triene **7** generated from **6** via an acid-promoted 1,3-H shift using 10 mol % of *p*-TsOH.

Scheme 2. Complication with the 1,5-H Shift into Conjugation



We quickly made a minor substrate adjustment to prevent such 1,5-H shift, but that led to the second unexpected finding as shown in Scheme 3. Heating α-prenylated allenamide **10a** led to a mixture of two ring-closure products: the desired 2-amido diene **13a** and the unexpected 1-amido diene **14a**

Scheme 3. Unexpected Competing 1,7-H Shift



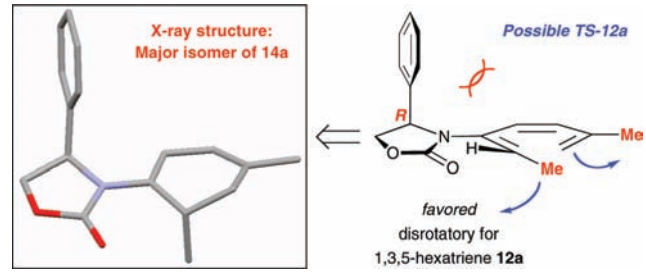


Figure 1. Torquoselective disrotatory ring closure.

in 1:4.5 ratio with **14a** being a 10:1 diastereomeric mixture. The latter implied the presence of amido triene **12a**, which could be rationalized through an antarafacial 1,7-H shift[9,17] from the initial amido triene **11a**, via the methyl group (in red) *syn* to the terminal olefin (in blue). More importantly, stereochemistry for the major isomer of **14a** could be assigned using its single-crystal X-ray structure (Figure 1). This unambiguous assignment suggests that a favored disrotatory course could proceed through the transition state as shown for amido triene **12a**.

(5) For recent reports on allenamide chemistry in 2009, see: (a) Hashimoto, K.; Horino, Y.; Kuroda, S. *Heterocycles* **2010**, *80*, 187. (b) Persson, A. K. Å.; Johnston, E. V.; Bäckvall, J.-E. *Org. Lett.* **2009**, *11*, 3817. (c) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (d) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547. (e) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett.* **2009**, *11*, 1563. (f) Broggini, G.; Galli, S.; Rigamonti, M.; Sottocornola, S.; Zecchi, G. *Tetrahedron Lett.* **2009**, *50*, 1447. (g) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (h) Lu, T.; Hayashi, R.; Hsung, R. P.; DeKorver, K. A.; Lohse, A. G.; Song, Z.; Tang, Y. *Org. Biomol. Chem.* **2009**, *9*, 3331. (i) Kimber, M. C. *Org. Lett.* **2010**, DOI: 10.1021/ol1001494.

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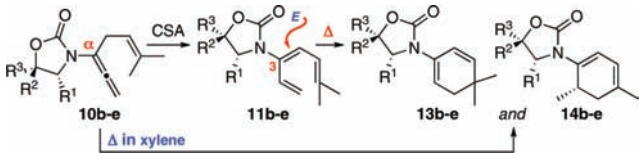
(8) For examples of allenamide isomerizations, see: (a) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807. Also see: (b) Farmer, M. L.; Billups, W. E.; Greenlee, R. B.; Kurtz, A. N. *J. Org. Chem.* **1966**, *31*, 2885. For an allenamide isomerization via Grubb's catalyst, see: (c) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045. (d) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117.

(9) For reviews for pericyclic ring closures, 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. For reviews on ring-closure in natural product synthesis, see: (c) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409. (d) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(10) For examples, 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.

Table 1. Tandem 1,3-H−1,7-H Shift Pericyclic Ring Closure



entry	α-prenyl allenamides	amido-trienes[a]	yield [%]:[c] 13	14 [dr[d]]
1	**10b**: R^1 = Bn $R^2 = R^3$ = H	**11b** [79]	-	50 [15:1]
2	**10c**: R^1 = *i*-Pr $R^2 = R^3$ = H	**11c** [91]	-	50 [15:1]
3	**10d**: R^1 = Me R^2 = Ph; R^3 = H	**11d** [74]	-	54 [9:1]
4	**10e**: R^1 = Ph $R^2 = R^3$ = Ph	**11e** [86]	15	45 [6:1]
5	**10b**: R^1 = Bn $R^2 = R^3$ = H		-	52 [15:1]
6	**10c**: R^1 = *i*-Pr $R^2 = R^3$ = H		-	62 [15:1]
7	**10d**: R^1 = Me R^2 = Ph; R^3 = H		21	38 [9:1]
8	**10e**: R^1 = Ph $R^2 = R^3$ = Ph		11	34 [6:1]

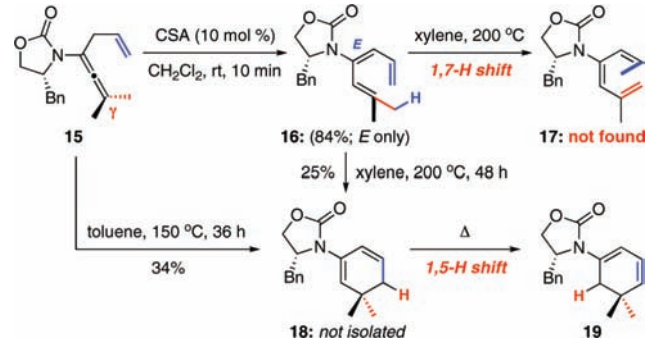
Δ in xylene[b]; *1,7-H shift–ring-closure*

Δ in xylene[b]; *tandem 1,3-H–1,7-H shift –ring-closure*

[a] All 3-amido trienes **11b**−**e** were attained from the respective allenamides **10b**−**e** via 1,3-H shift promoted by CSA (10 mol %). Reactions were run in CH_2Cl_2 at rt for 10 min, and isolated yields are shown in the respective brackets. [b] For all entries: conc = 0.10 M; temp = 135 °C; time = 20 h. [c] Isolated yields. [d] Ratios determined by ^{1}H and/or ^{13}C NMR.

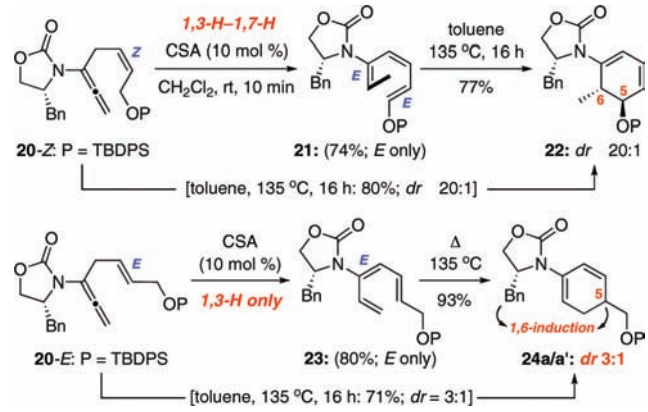
The tandem 1,3-H-1,7-H shift appears to be general whether commencing from amido trienes **11b**−**e** (entries 1−4 in Table 1) or directly from α-prenylated allenamides **10b**−**e** (entries 5−8). It is noteworthy that in the case of allenamide **10b** and **10c** cyclic amido dienes **14b** and **14c** were the only products resulting from a tandem 1,3-H−1,7-H shift−pericyclic ring closure. In addition, there was no equilibration between **13** and **14** under the reaction conditions.[18]

Scheme 4. Directional Preference in the 1,7-H Shift



Probing further mechanistically, we found two phenomena associated with this 1,7-H shift process. First, heating either triene **16**, derived from γ-substituted allenamideto no observable 1,7-H shift with cyclic diene **19** as the only identifiable product. Isolation of **19** implies the ring closure of triene **16** had taken place to give **18** followed by 1,5-H shift (Scheme 4). This experiment suggests that there exists a directional preference for the 1,7-H shift in these amido trienes and that it is not sufficient simply having a methyl group (in red) at one terminus of the triene *syn* to the other terminus (in blue).

Scheme 5. Diverging Tandem Pathway: *E*- vs *Z*-Olefin



Second, we found a distinct dependence of the 1,7-H shift on the olefinic geometry. As shown in Scheme 5, reactions of allenamides **20**-*Z* and **20**-*E* proceeded through distinctly different tandem pathways. **15**, or **15** led While 1,3-H−1,7-H shift occurred with **20**-*Z* en route to cyclic amido diene **22** via pericyclic ring closure of triene **21**, the reaction of

(11) For some examples on recent 6-π-electron electrocyclic ring closures of 1,3,5-hexatrienes, see: (a) Bishop, L. M.; Barbarow, J. E.; Bergmen, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100. (b) Sofiyev, V.; Navarro, G.; Trauner, D. *Org. Lett.* **2008**, *10*, 149. (c) Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323. (d) Hulot, C.; Blong, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046. (e) Benson, C. L.; West, F. G. *Org. Lett.* **2007**, *9*, 2545. (f) Pouwer, R. H.; Schill, H.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2007**, 4699. (g) Jung, M. E.; Min, S.-J. *Tetrahedron* **2007**, *63*, 3682.

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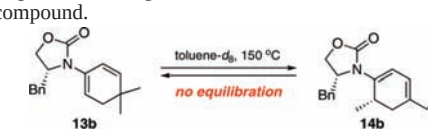
(14) (a) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117. (b) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081.

(15) Xiong, H.; Hsung, R. P.; Wei, L.-L.; Berry, C. R.; Mulder, J. A.; Stockwell, B. *Org. Lett.* **2000**, *2*, 2869.

(16) See the Supporting Information.

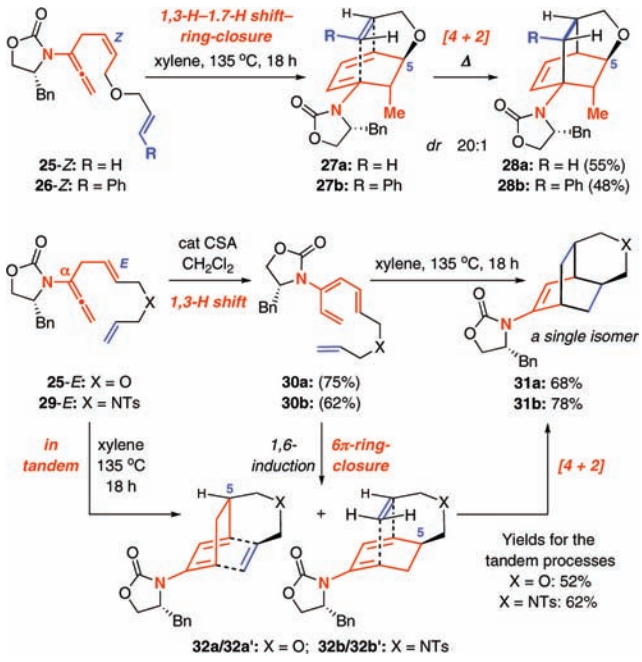
(17) For recent examples in thermal antarafacial 1,7-H shift of 1,3,5-hexatrienes, see: (a) Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457. (b) Mousavipour, S. H.; Fernández-Ramos, A.; Meana-Pañeda, R.; Martínez-Núñez, E.; Vázquez, S. A.; Ríos, M. A. *J. Phys. Chem. A* **2007**, *111*, 719. (c) Gu, Z.; Ma, S. *Chem.—Eur. J.* **2008**, *14*, 2453. (d) Shu, X.-Z.; Ji, K.-G.; Zhao, S.-C.; Zheng, Z.-J.; Chen, J.; Lu, L.; Liu, X.-Y.; Liang, Y.-M. *Chem.—Eur. J.* **2008**, *14*, 10556.

(18) Independent heating of **13b** or **14b** led to no observable amount of the other compound.



allenamide **20**-*E* gave **24** with no observable 1,7-H shift. Relative stereochemistry in **22** was assigned on the basis of a disrotatory ring closure, while the absolute stereochemistry was assessed on the basis of **14a**. Cyclic amido diene **24** was found as a 3:1 isomeric mixture with respect to C5, thereby implying that albeit modest and unassigned at this time,[19]a rather impressive 1,6-asymmetric induction took place during the ring closure.

Scheme 6. In Tandem with [4 + 2] Cycloaddition



To both accentuate this dichotomy and render these stereoselective ring closures synthetically useful, we embarked on tandem processes that would include [4 + 2] cycloadditions. As shown in Scheme 6, reactions of allenamides **25**-*Z* and **26**-*Z* led to tricycles **28a** and **28b** as a single isomer through a highly stereoselective [4 + 2] cycloaddition of cyclic amido dienes **27a** and **27b**, respectively, thereby constituting a quadruple tandem process of 1,3-H−1,7-H shift−6π-electron pericyclic ring-closure−[4 + 2] cycloaddition. Stereochemical outcome of the cycloaddition was controlled through the C5-stereocenter, which was installed during the torquoselective ring closure.

(19) Attempts were made to attain an X-ray but were not successful mainly because of difficulties in the separation of diastereomers. Further efforts are ongoing.

(20) Unfortunately, Diels−Alder cycloadditions of **32a/a′** or **32b/b′** in Scheme 6 did not provide conclusive insight into the stereochemical outcome of ring closures of **30a** and **30b**.

In contrast, reactions of allenamides **25**-*E* (for a direct comparison with **25**-*Z*) and **29**-*E* led the respective tricycles **31a** and **31b** (assigned via X-ray: see Figure 2) in excellent yields and high diastereoselectivity proceeding from amidotrienes **30a** and **30b** or directly from the allenamides in a triple tandem process. In either case, the [4 + 2] cycloaddition presumably went through the diastereomeric pairs **32a/a′** (X = O) and **32b/b′** (X = NTs) given the modest 1,6-induction found for **20**-*E*. It is noteworthy that despite not having assigned these diastereomers with ratios undermined,[20] both pairs would actually converge to give **31a** and **31b**, respectively. These tandem processes provide a rapid assembly of complex tricycles from very simple allenamides, thereby manifesting their tremendous power and synthetic potential.

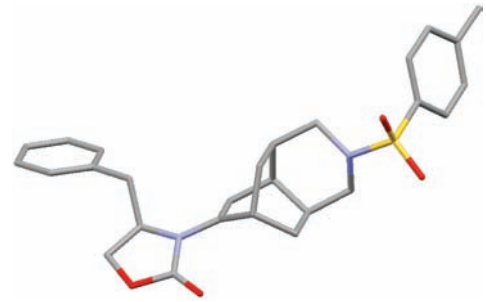


Figure 2. X-ray structure of **31b**.

We have described here a new torquoselective ring closure of chiral amide-substituted 1,3,5-hexatrienes and its application in tandem with [4 + 2] cycloaddition. The 1,3,5-hexatrienes were derived via either a 1,3-H or 1,3-H−1,7-H shift of α-substituted allenamides, and the entire sequence through the Diels−Alder could be in tandem from allenamides. Applications of these new tandem processes as well as mechanistic understanding and improvement of the observed 1,6-asymmetric induction are underway.

Acknowledgment. We thank the NIH (GM066055) for support and Dr. Victor Young (University of Minnesota) for X-ray structural analysis.

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.

OL902821W