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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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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.

Our intention was quickly met with two unexpected findings. Initially, when heating allenamide **6**^{14,15} in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at 135 °C, instead of isolating the desired amido-diene **8** from ring-closure of the triene **7**, we found **9**¹⁵ 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 % *p*-TsOH.

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

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Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

1-amido-diene **14a** 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**.

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

Probing further mechanistically, we found two phenomena associated with this 1,7-H shift process. Firstly, either heating triene **16**, derived from γ -substituted allenamide **15**, or **15** led to 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].

Secondly, 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. 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 allenamide **20-E** gave **24** with no observable 1,7-H shift. Relative stereochemistry in **22** was assigned based on a disrotatory ring-closure, while the absolute stereochemistry was assessed based on **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.

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.

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 amido-trienes **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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

19. Attempts were made to attain an X-ray but 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**.

Figure 1.
A Torquoselective Disrotatory-Ring Closure.

Figure 2.
X-Ray Structure of **31b**.

Scheme 1.
A New Torquoselective Pericyclic Ring-Closure.

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

Scheme 3.
An Unexpected Competing 1,7-H Shift.

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

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

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

Table 1

A Tandem 1,3-H–1,7-H Shift–Pericyclic Ring-Closure.

entry	α -prenyl allenamides	amido-trienes ^a	yield [%]: ^c	13	14 [<i>dr</i>] ^d
1	10b : R ¹ = Bn R ² = R ³ = H	11b [79]	in xylene^b 1,7-H shift– ring-closure	-	50 [$\geq 15:1$]
2	10c : R ¹ = <i>i</i> -Pr R ² = R ³ = H	11c [91]		-	50 [$\geq 15:1$]
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	in xylene^b tandem 1,3-H–1,7-H shift –ring-closure		-	52 [$\geq 15:1$]
6	10c : R ¹ = <i>i</i> -Pr R ² = R ³ = H			-	62 [$\geq 15:1$]
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]

^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 CH₂Cl₂ at rt for 10 min, and isolated yields are shown in the respective brackets.

^b For all entries: *concn* = 0.10 M; temp = 135 °C; time = 20 h.

^c Isolated yields.

^d Ratios determined by ¹H and/or ¹³C NMR.