Bio-inspired polyene cyclization: aziridinyl polyene cyclization catalyzed by $InBr_3$†

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This communication describes a highly efficient aziridinyl polyolefin cyclization catalyzed by $InBr_3$ to synthesize chiral terpenoid bearing a 3-amino group in the A ring; both good yields and excellent asymmetric induction were achieved.

The efficiency exhibited by epoxy-squalene cyclase has continued to intrigue chemists over the decades.[1] Therefore, there have been many efforts directed toward the mechanistic understanding as well as development of new methods which can mimic this fascinating biological process.[2] Inspired by the epoxy-squalene cyclase, we are interested in the analogous aziridine initiated polyene cyclization. If successful, this aziridine initiated polyene cyclization will provide easy access to a wide variety of biologically interesting aza-terpenes.[3] However, despite recent advances in the development of new bio-inspired polyene cyclizations using different initiating groups,[4,5] to the best of our knowledge, there is no report on the aziridine[6] initiated polyene cyclization. In addition, cationic biomimetic polyene cyclizations promoted by a catalytic amount of promoter are still rare.[7] In this communication, we document a catalytic bio-inspired polyene cyclization using aziridinyl polyolefins as the starting precursors catalyzed by $InBr_3$. Both the tricyclic and tetracyclic terpenoids were obtained in good yields with excellent diastereoselectivities.

Our initial efforts were focused on finding proper reaction conditions to promote the cyclization of aziridinyl olefin[8,9] **1**, and the results are summarized in Table 1.‡ We found that 0.2 equivalents of $InBr_3$ successfully catalyzed the cyclization of **1** to afford tricyclic compound **2** in 69% yield as a single isomer (Table 1, entry 3). The relative stereochemistry of the cyclization product was elucidated by a single-crystal X-ray analysis as depicted in Fig. 1 (ESI†). When less $InBr_3$ (<0.2 equiv.) was used, the cyclization products were obtained in lower yield. TfOH (2.0 equivalents) was also found to promote the cyclization smoothly to furnish **2** in 62% yield (Table 1, entry 1), but the yield decreased to 30% when the amount of TfOH was reduced to 0.2 equivalents. On the other hand, other indium salts catalyzed the cyclization reaction to afford the desired product in lower yields (entries 6 and 7). Other Lewis acids, such as $La(OTf)_3$, were found to be less effective, affording the cyclization product in even lower yield (entry 8).

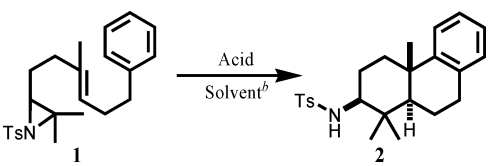
With the optimized reaction conditions in hand, various aziridinyl olefin substrates were carried out to provide a wide variety of 3-amino substituted tricyclic terpenoids,[3] and the results are summarized in Table 2. In all cases, good yields and excellent diastereoselectivities (single isomer) were achieved.

Based on the encouraging results from the tricyclic formation of aziridinyl olefin **1** catalyzed by $InBr_3$, we further explored the scope of aziridinyl olefin substrates **3**, and the results are summarized in Table 3. In all cases, moderate to good yields with good diastereoselectivities were achieved for tetracyclic cyclization products (Table 3, entries 1 to 5).

The relative stereochemistry of cyclization product **4d** was again elucidated by a single-crystal X-ray analysis as depicted in Fig. 2 (ESI†).

Next, we explored the asymmetric version of aziridinyl olefin cyclization with enantiomerically-enriched substrate **8**[8,10] (97% ee) as shown in Scheme 1. Cbz group was used instead of Ts group to facilitate the removal of the nitrogen protecting group at a later stage. Compound **8** was synthesized from known epoxide[5d] **5** over three steps in 25% yield without loss of enantiomeric purity. To this end, the aziridinyl olefin **8** was subjected to 0.2 equivalents of $InBr_3$ for 2 hours at room temperature in CH_2Cl_2, and the cyclization product **9** was obtained in 67% yield with 97% ee indicating retention of the enantiomeric purity of the cyclization starting material in the

Table 1 Aziridinyl olefin cyclization promoted by various catalysts[a]



1 2

Entry	Acid	Equiv.	T/°C	Solvent	Yield (%)[c]
1	TfOH	2.0	rt	CH_2Cl_2	62
2	$InBr_3$	2.0	rt	CH_2Cl_2	65
3	*$InBr_3$*	*0.2*	*rt*	*CH_2Cl_2*	*69*
4	$InBr_3$	0.2	−20	CH_2Cl_2	Trace[d]
5	$InBr_3$	0.2	rt	PhMe	58
6	$InCl_3$	0.2	rt	CH_2Cl_2	28[d]
7	$In(OTf)_3$	0.2	rt	CH_2Cl_2	33[e]
8	$La(OTf)_3$	0.2	rt	CH_2Cl_2	Trace[d]

[a] Conditions: acid and substrate **1** (1.0 equiv., 0.025 M, solvent) were mixed and stirred at room temperature for 2 hours. [b] CH_2Cl_2 was used as solvent except for entry 5. [c] Isolated yield. [d] Starting material was recovered after reaction. [e] Unknown side product was isolated.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, ^1H NMR, ^{13}C NMR and analytical data for all compounds. CCDC 715056 and 715057 for **2** and **4d**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b903696b

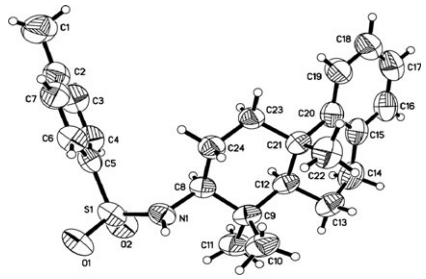
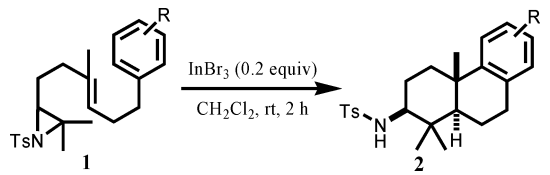


Fig. 1 Single-crystal X-ray structure (50% ellipsoids) of cyclization product **2** (ESI†).

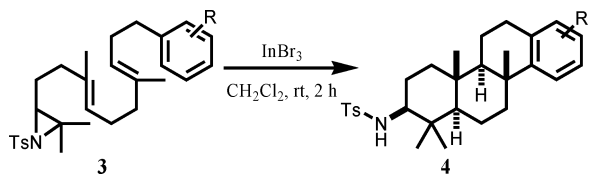
Table 2 Synthesis of tricyclic terpenoids using $InBr_3$ catalyzed aziridinyl olefin cyclization[a]



Entry	R	Substrate	Product	Yield (%)[b]
1	—	**1**	**2**	69
2	4-Me	**1a**	**2a**	70
3	4-OMe	**1b**	**2b**	75
4	4-*i*-Pr	**1c**	**2c**	74
5	2-Me	**1d**	**2d**	70

[a] Conditions: $InBr_3$ (0.2 equiv.) and substrate **1** (1.0 equiv., 0.025 M, CH_2Cl_2) were mixed and stirred at room temperature for 2 hours. [b] Isolated yield.

Table 3 Synthesis of tetracyclic terpenoids using $InBr_3$ catalyzed aziridinyl polyolefin cyclization[a]



Entry	R	Substrate	Product[b]	Equiv.	Yield (%)[c]	Ratio[d]
1	—	**3**	**4**	0.2	63	82 : 18
2	4-Me	**3a**	**4a**	0.2	51	84 : 16
3	4-OMe	**3b**	**4b**	0.2	55	87 : 13
4	3-Me	**3c**	**4c**	0.2	52	87 : 13
5	2-Me	**3d**	**4d**	0.2	65	86 : 14
6	2-Me	**3d**	**4d**	2.0	62	88 : 12

[a] Conditions: $InBr_3$ (0.2 equiv.) and substrate **3** (1.0 equiv., 0.025 M, CH_2Cl_2) were mixed and stirred at room temperature for 2 hours. [b] Bicyclized isomers were obtained. See ESI†. [c] Combined yields of desired product and bicyclized isomers. [d] Desired tetracyclic product (major) and bicyclized isomers (minor) ratios were determined by ^1H NMR and ^{13}C NMR. The ratio was not improved after treating with TfOH at room temperature for 12 hours.

final cyclization product. In addition, the cyclization product **9** was further functionalized into primary amine **10**, which provides a practical approach to the synthesis of biologically

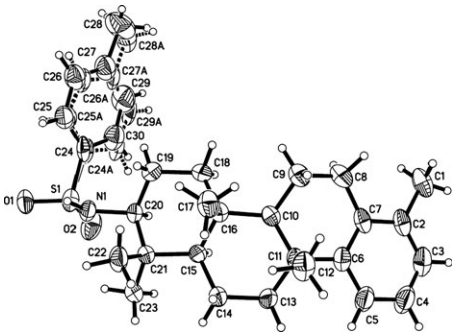
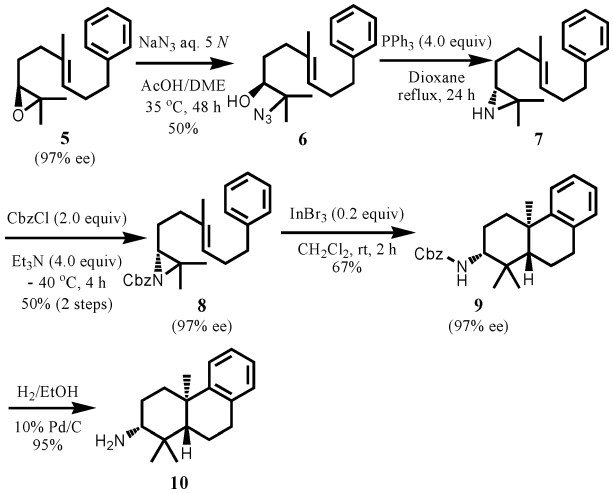


Fig. 2 Single-crystal X-ray structure (50% ellipsoids) of tetracyclic cyclization product **4d** (ESI†).



Scheme 1 $InBr_3$ catalyzed asymmetrical aziridinyl olefin cyclization.

active chiral terpenoid compounds bearing a 3-amino group in the A ring.[3]

In conclusion, we have demonstrated an aziridinyl polyolefin cyclization promoted by catalytic amounts of $InBr_3$. In contrast to epoxide initiated polyene cyclization, it is surprising to note that this aziridine initiated polyene cyclization works well with a catalytic amount of Lewis acid. Both good yields and good diastereoselectivities were obtained for the A ring 3-amino substituted tricyclic and tetracyclic terpenoid compounds. When an enantiomerically-enriched cyclization substrate was used, retention of the enantiomeric purity of the cyclization starting material was achieved. We believe that this process would allow rapid and efficient access to chiral terpenoid compounds bearing a 3-amino group in the A ring. The applications of this method to the synthesis of diverse compounds as well as total synthesis are currently in progress in our group.

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Notes and references

‡ *Representative procedure*: to a 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InBr_3$ (7 mg, 0.02 mmol, 0.20 equiv.). CH_2Cl_2 (1.5 mL) was added *via* syringe. Aziridinyl olefin substrate **1** (40 mg, 0.1 mmol, 1.0 equiv.) was added as CH_2Cl_2

solution *via* syringe. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched by aqueous $NaHCO_3$ (5 mL) saturated solution. The mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired amine product as a colorless solid in 69% yield. Mp: 223.5–225 °C. R_f: 0.50 (hexane–ethyl acetate = 4 : 1). ^{1}H NMR (400 MHz, $CDCl_3$): 7.78–7.72 (m, 2H), 7.31–7.26 (m, 2H), 7.16–6.98 (m, 4H), 4.27 (d, J = 9.33 Hz, 1H), 2.97–2.89 (m, 2H), 2.89–2.78 (m, 1H), 2.43 (s, 3H), 2.19 (dt, J = 13.10, 3.10 Hz, 1H), 1.86 (dd, J = 13.27, 7.39 Hz, 1H), 1.75–1.65 (m, 1H), 1.60–1.53 (m, 1H), 1.51–1.45 (m, 1H), 1.44–1.36 (m, 1H), 1.35–1.28 (m, 1H), 1.11 (s, 3H), 0.90 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 148.7, 143.2, 138.1, 134.8, 129.6, 128.9, 127.1, 125.7, 125.5, 124.3, 62.0, 50.8, 38.2, 37.6, 37.2, 30.5, 28.1, 26.7, 24.7, 21.5, 19.2, 16.2. HRMS (ESI): m/z calculated for $C_{24}H_{32}NO_2S$ $[M + H]^+$: 398.2159, found: 398.2154. FTIR (NaCl): ν 3462 (br), 2957, 2928, 1700 (br), 1645 (br), 1450, 115 cm^{-1}.

1 (*a*) R. G. Langdon and K. Bloch, *J. Am. Chem. Soc.*, 1952, **74**, 1869–1870; (*b*) R. B. Woodward and K. Bloch, *J. Am. Chem. Soc.*, 1953, **75**, 2023–2024; (*c*) E. J. Corey, W. E. Russey and P. R. O. Montellano, *J. Am. Chem. Soc.*, 1966, **80**, 4750–4751; (*d*) E. E. van Tamelen, J. Willet, M. Schwartz and R. Nadeau, *J. Am. Chem. Soc.*, 1966, **80**, 5937–5938.

2 For reviews on biomimetic polyene cyclization, see: (*a*) P. A. Bartlett, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, New York, 1984, vol. 3, p. 341; (*b*) R. A. Yoder and J. N. Johnston, *Chem. Rev.*, 2005, **105**, 4730–4756.

3 Chiral terpenoid alkaloids bearing a 3-amino group in the A ring often have significant biological activities: (*a*) S. Ijichi and S. Tamagaki, *Chem. Lett.*, 2005, 356–357; (*b*) I. Sun, H. Wang, Y. Kashiwada, J. Shen, L. M. Cosentino, C. H. Chen, L. M. Yang and K. H. Lee, *J. Med. Chem.*, 1998, **41**, 4648–4657; (*c*) C. Ma, N. Nakamura and M. Hattori, *Chem. Pharm. Bull.*, 2000, **48**, 1681–1688; (*d*) R. D. Goff and J. S. Thorson, *Org. Lett.*, 2009, **11**, 461–464.

4 (*a*) Y. J. Zhao and T. P. Loh, *J. Am. Chem. Soc.*, 2008, **130**, 10024–10029; (*b*) Y. J. Zhao and T. P. Loh, *Org. Lett.*, 2008, **10**, 2143–2145; (*c*) Y. J. Zhao, S. S. Chng and T. P. Loh, *J. Am. Chem. Soc.*, 2007, **129**, 492–493; (*d*) Y. J. Zhao and T. P. Loh, *Chem. Commun.*, 2008, 1434–1436.

5 Recent reports on biomimetic epoxy olefin cyclization: (*a*) D. C. Behenna and E. J. Corey, *J. Am. Chem. Soc.*, 2008, **130**, 6720–6721; (*b*) A. X. Huang, Z. Xiong and E. J. Corey, *J. Am. Chem. Soc.*, 1999, **121**, 9999–10003; (*c*) M. Bogenstätter, A. Limberg, L. E. Overman and A. L. Tomasi, *J. Am. Chem. Soc.*, 1999, **121**, 12206–12207; (*d*) J. F. Zhao, Y. J. Zhao and T. P. Loh, *Chem. Commun.*, 2008, 1353–1355; (*e*) J. Justicia, J. L. Oller-Lopez, A. G. Campaña, J. E. Oltra, J. M. Cuerva, E. Buñuel and D. J. Cardenas, *J. Am. Chem. Soc.*, 2005, **127**, 14911–14921; (*f*) J. Justicia, J. E. Oltra, A. F. Barrero, A. Guadaño, A. González-Coloma and J. M. Cuerva, *Eur. J. Org. Chem.*, 2005, 712–718; (*g*) J. Justicia, J. E. Oltra and J. M. Cuerva, *J. Org. Chem.*, 2004, **64**, 5803–5806; (*h*) J. D. Rainier and A. B. III Smith, *Tetrahedron Lett.*, 2000, **41**, 9419–9423; (*i*) J. D. Neighbors, N. R. Mente, K. D. Boss, D. W. Zehnder and D. F. Wiemer, *Tetrahedron Lett.*, 2008, **41**, 516–519; (*j*) E. E. van Tamelen and J. R. Hwu, *J. Am. Chem. Soc.*, 1983, **105**, 2490–2491.

6 (*a*) For reviews on the selective opening of aziridines and azirines, see: A. Padwa, M. C. McMills, S. C. Bergmeier, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, Elsevier Press, Amsterdam, 2008, vol. 1, p. 2 and 105, and references therein; (*b*) For reviews on related *N*-acyliminium initiated polyene cyclizations, see: H. Hiemstra, W. N. Speckamp, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 2, ch. 4.5, p. 1047; (*c*) J. Dijkink and W. N. Speckamp, *Tetrahedron Lett.*, 1977, **18**, 935–938; (*d*) J. Dijkink and W. N. Speckamp, *Tetrahedron*, 1978, **34**, 173–178.

7 No example of the catalytic epoxy olefin cyclization has been reported so far. A few of catalytic cases of variant polyene cyclization have been reported: (*a*) J. A. Feducia and M. R. Gagné, *J. Am. Chem. Soc.*, 2008, **129**, 11880–11881; (*b*) C. A. Mullen, A. N. Campbell and M. R. Gagné, *Angew. Chem., Int. Ed.*, 2008, **47**, 6011–6014 and references therein; (*c*) A. Sakakura, A. Ukai and K. Ishihara, *Nature*, 2007, **445**, 900–903; (*d*) M. Uyanik, K. Ishihara and H. Yamamoto, *Org. Lett.*, 2006, **8**, 5649–5652; (*e*) D. Yang, S. Gu, Y. L. Yan, N. Y. Zhu and K. K. Cheung, *J. Am. Chem. Soc.*, 2001, **123**, 8612–8613; (*f*) D. Yang, S. Gu, Y. L. Yan, H. W. Zhao and N. Y. Zhu, *Angew. Chem., Int. Ed.*, 2002, **41**, 3014–3017; (*g*) H. Yamamoto, I. Sasaki, Y. Hirai, K. Namba, H. Imagawa and M. Nishizawa, *Angew. Chem., Int. Ed.*, 2009, **48**, 1244–1247.

8 (*a*) D. Van Ende and A. Krief, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 279–280; (*b*) L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto and J. E. Anderson, *J. Am. Chem. Soc.*, 1971, **93**, 1815 and references therein.

9 (*a*) T. Manaka, S. I. Nagayama, W. Desadee, N. Yajima, T. Kumamoto, T. Watanabe, T. Ishikawa, M. Kawahata and K. Yamaguchi, *Helv. Chim. Acta*, 2007, **90**, 128–142; (*b*) J. S. Yadav, B. V. S. Reddy and G. Parimala, *Synlett*, 2002, 1143–1145; (*c*) S. Peruncheralathan, M. Henze and C. Schneider, *Tetrahedron Lett.*, 2007, **48**, 6743–6746; (*d*) J. S. Yadav, B. V. S. Reddy, K. V. Rao, K. S. Raj and A. R. Prasad, *Synthesis*, 2002, 1061–1064; (*e*) J. S. Yadav, B. V. S. Reddy and G. M. Kumar, *Synlett*, 2001, 1417–1418.

10 Chiral azido alcohol was synthesized according to known procedures: (*a*) F. Fringuelli, O. Poermatti, F. Pizzo and L. Vaccaro, *J. Org. Chem.*, 1999, **64**, 6094–6096; (*b*) M. V. Voronkov, A. V. Gontcharov, R. C. Kanamarlapudi, P. F. Richardson and Z. M. Wang, *Org. Process Res. Dev.*, 2005, **9**, 221–224.

