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One-Pot Synthesis of Aminoenone via Direct Reaction of the Chloroalkyl Enone with NaN_3: Rapid Access to Polycyclic Alkaloids

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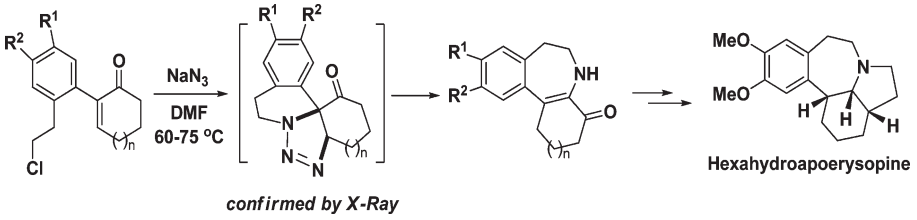

A new one-pot procedure for the preparation of aminoenone from chloroalkyl enone and sodium azide was demonstrated. The structure of the presumed triazoline intermediate in this process was confirmed by X-ray analysis for the first time. As the application of this methodology, the synthesis of polycyclic alkaloid hexahydroapoerysopine (**1a**) was achieved through an efficient synthetic route.

Introduction

Aminoenone (including α-aminoenone and *β*-aminoenone) as nitrogen-contained versatile building blocks are exhibiting more and more utilities for preparation of many biologically important organic molecules,[1] and also, they are often endowed with useful pharmacological properties.[2] Several approaches have been developed to achieve these units;[1a,e] however, more efficient and practical approaches are still required. Rearrangements related to azides have played an extensive role in the preparation of nitrogen heterocyclic compounds.[3] As one part of this pioneering research, the intramolecular reaction of alkyl azide with enone has been investigated since the early 1980s, with important contributions made by Schultz, Sha, and Molander, among others.[4] Much of the earlier research was focused on mechanistic issues related to the breakdown of the presumed triazoline intermediates. Although these investigations have greatly developed the azide chemistry, there still remain some problems especially on the direct experimental evidence of triazoline intermediate and mild condition of this transformation. In 2003, Aubé and co-workers reported an elegant Lewis acid promoted intermolecular reaction of alkyl azide with enone (Scheme 1a).[5] In most cases, the products obtained from the reaction were interesting *β*-aminoenones, which might be formed via a [3+2] cycloaddition-ring contraction process. According to this hypothesis, only *β*-aminoenone

(1) (a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294. (b) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 207–343. (c) Cimarelli, C.; Palmieri, G. *Recent Res. Dev. Org. Chem.* **1997**, *1*, 179–189. (d) Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979–988. (e) Elassara, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463–8480. (f) Ferraz, H. M. C.; Goncalo, E. R. S. *Quim. Nova* **2007**, *30*, 957–964.

(2) (a) Scott, K. R.; Rankin, G. O.; Stables, J. P.; Alexander, M. S.; Edafiogho, I. O.; Farrar, V. A.; Kolen, K. R.; Moore, J. A.; Sims, L. D.; Tonnu, A. D. *J. Med. Chem.* **1995**, *38*, 4033–4043. (b) Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159–175. (c) Edafiogho, I. O.; Moore, J. A.; Alexander, M. S.; Scott, K. R. *J. Pharm. Sci.* **1994**, *83*, 1155–1170. (d) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417–436. (e) Edafiogho, I. O.; Kombian, S. B.; Ananthalakshmi, K. V. V.; Salama, N. N.; Eddington, N. D.; Wilson, T. L.; Alexander, M. S.; Jackson, P. L.; Hanson, C. D.; Scott, K. R. *J. Pharm. Sci.* **2007**, *96*, 2509–2531.

(3) Resent review see: (a) Lang, S.; Murphy, J. *Chem. Soc. Rev.* **2006**, *35*, 146–156. (b) Stefan, B.; Carmen, G.; Kerstin, K.; Viktor, Z. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188–5240.

(4) (a) Schultz, A. G.; Ravichandran, R. *J. Org. Chem.* **1980**, *45*, 5008–5009. (b) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676–1678. (c) Sha, C. K.; Ouyang, S. L.; Hsieh, D. Y.; Hseu, T. H. *J. Chem. Soc., Chem. Commun.* **1984**, 492–494. (d) Sha, C. K.; Yuang, J. J.; Ouyang, S. L. *Heterocycles* **1984**, 566. (e) Sha, C. K.; Ouyang, S. L.; Hsieh, D. Y.; Chang, R. C.; Chang, S. C. *J. Org. Chem.* **1986**, *51*, 1490–1494. (f) Schultz, A. G. *Adv. Cycloaddit.* **1988**, *1*, 53. (g) Molander, G. A.; Hiersemann, M. *Tetrahedron Lett.* **1997**, *38*, 4347–4350. (h) Molander, G. A.; Christopher, T. B. *Tetrahedron Lett.* **2002**, *43*, 5385–5388.

(5) Reddy, D. S.; Judd, W. R.; Aube, J. *Org. Lett.* **2003**, *5*, 3899–3902. Interestingly, acyclic enones gave different products under similar conditions, see: Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354–1355.

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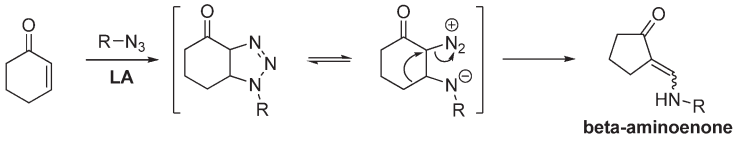
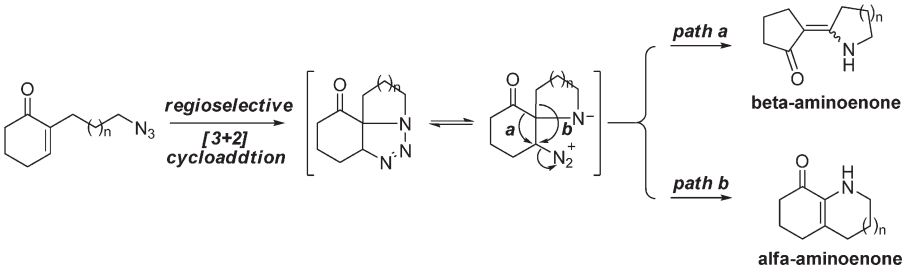
SCHEME 1. Tandem [3+2] Cycloaddtion/Rearrangement

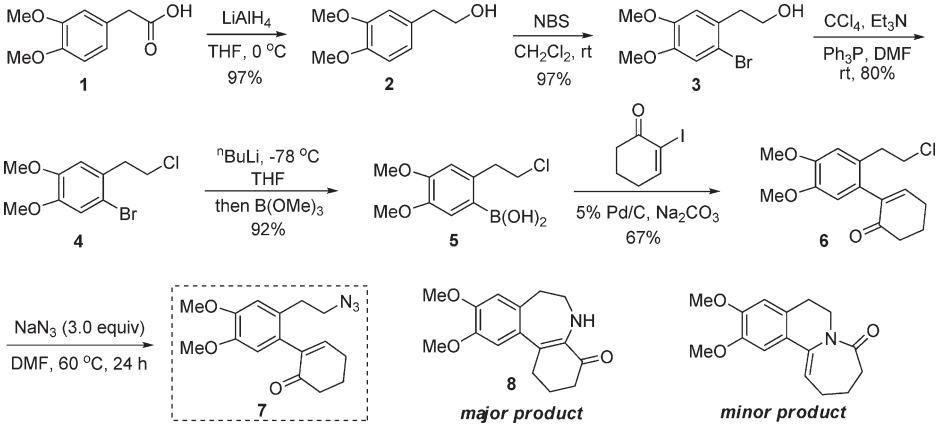
a. Lewis acid promoted intermolecular [3+2] cycloaddition-ring contraction.



b. Designed intramolecular [3+2] cycloaddition-rearrangement to α-aminoenone.



SCHEME 2. Preparation of Arylazide Enone Substrate 7



could be formed. Inspired by this result, we envisioned that the α-aminoenone could be formed (Scheme 1b, path b vs path a) if the regioselectivity of the [3+2] cycloaddition[6] was reversed.[7] Herein, we present the designed tandem [3+2] cycloaddtion/rearrangement leading to α-aminoenone, together with it is application to the synthesis of polycyclic alkaloid.

Results and Discussion

Our strategy of constructing α-aminoenone relied on a tandem regioselective [3+2] cycloaddtion/1,2-migration. For this approach to be successful, there were two central issues to be addressed: (1) Could the triazoline intermediate and zwitterionic species be formed during the process? (2) How could the regioselectivity of the 1,2-migration be controlled in order to drive the rearrangement through path b over path a. Because an electron-donating aromatic ring has a stronger migratory aptitude over many other groups,[8] arylazide enone **7** was prepared for this envisage as the model substrate.

As depicted in Scheme 2, reduction of Homoveratric acid **1** with $LiAlH_4$ gave alcohol **2**. Bromation and subsequent chlorination of **2** afforded **4** in 78% overall yield. Treatment of **4** with ^{n}BuLi and $B(OMe)_3$ at −78 °C gave aryl boracic acid **5** in 92% yield. The Suzuki−Kumada coupling of **5** and 2-iodocyclohexenone afforded enone **6** in 67% yield. We tried to prepare substrate **7** by heating a mixture of chloride **6** and NaN_3 (3.0 equiv) in dry DMF at 60 °C for 24 h. We found that it directly gave the α-aminoenone **8** as the major product along with a trace of **7** and the minor enamide-type product.[9]

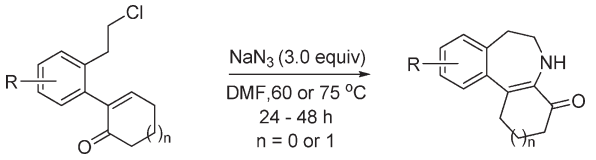
(6) Such 1,3-cycloaddition of alkylazide enone to triazoline was presumed in the literature, but chemists have never observed this intermediate up until the present moment.

(7) For the decomposition of nonpolarized triazoline, see: (a) Wladkowski, B. D.; Smith, R. H.; Michejda, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 7893–7897. (b) Smith, R. H.; Wladkowski, B. D.; Taylor, J. E.; Thompson, E. J.; Pruski, B.; Klose, J. R.; Andrews, A. W.; Michejda, C. J. *J. Org. Chem.* **1993**, *58*, 2097–2103. (c) Schmidt, B. F.; Snyder, E. J.; Carroll, R. M.; Farnsworth, D. W.; Michejda, C. J.; Smith, R. H. *J. Org. Chem.* **1997**, *62*, 8660–8665. For the decomposition of polarized triazoline, see: Hong, K. B.; Donahue, M. G.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 2323–2328.

(8) Initially, we thought that the migration attitude between the aryl group and acyl group would play an important role in the regioselectivity during this process.

(9) Interestingly, Molander et al. had observed[4h] that, treatment of the analogue of **7** in xylenes under reflux condition for 18−24 h gave enamides as sole products.

TABLE 1. One-Pot Strategy to α-Aminoenone[a]



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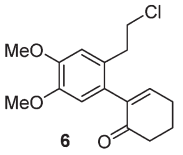
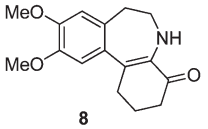
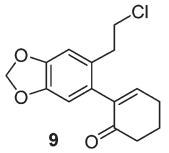
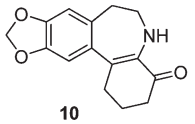
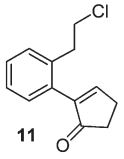
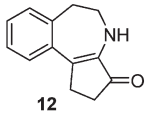
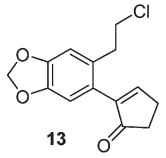
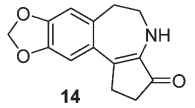
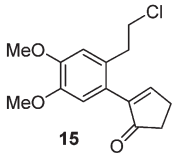
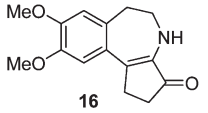
1	 **6**	75	 **8**	47%
2	 **9**	75	 **10**	42%
3	 **11**	60	 **12**	81%
4	 **13**	60	 **14**	95%
5	 **15**	60	 **16**	71%

[a]General reaction condition: a mixture of chloroalkyl enone (0.2 mmol) and NaN_3 (0.6 mmol) in DMF (3 mL) was stirred at 60 or 75 °C under argon atmosphere until the corresponding alkylazide enone disappeared (determined by TLC analysis). [b]Isolated yield.

The structure of α-aminoenone **8** was assigned by comparation of NMR spectra to the analogue **14**, which was confirmed by X-ray analysis (see further for details). Although the yield was not excellent, this unexpected result indicated that the tandem intramolecular [3+2] cycloaddition-rearrangement was feasible for preparation of α-aminoenone. Further screening of solvents revealed that it gave better results in polar aprotic solvents such as DMF or DMSO, while only azide **7** could be obtained when the reaction was performed in CH_3CN or nonpolar toluene. Additionally, this reaction was sensitive to the temperature. We found that it gave aminoenone **8** in dramatically lower yield when the temperature was increased to 100 °C.

As shown in Table 1, several arylchloroalkyl enone analogues[10] were prepared to investigate the efficiency of the reaction. To our delight, all substrates were proved to be effective in this reaction and the desired α-aminoenones were obtained in moderate to good yields. Generally, five-membered substrates gave better results than six-membered ones. Electron-donating substitutions on the aryl rings only slightly affected the yields. It should be noted that the five-membered substrates always gave a relatively stable intermediate under the reaction condition. The intermediates could be isolated and converted to the final α-aminoenone products slowly in the presence of water, while 2N aqueous HCl would accelerate the process. We were pleased to observe that the triazoline intermediate **17**[11] relevant to the α-aminoenone **14**[12] was stable in basic medium. Initially, we tried our best to obtain

(10) For the syntheses of substrates see the Supporting Information for details.

(11) The crystallographic coordinates for **17** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 742901. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/data_request/cif.

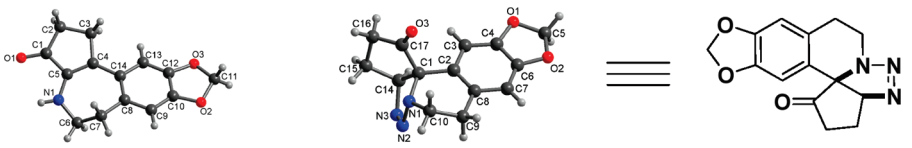


FIGURE 1. X-ray crystallography of compounds **14** and **17**.

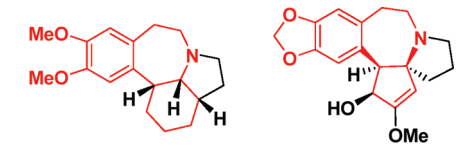


FIGURE 2. Representative polycyclic alkaloids with [5,7] and [6,7] ring-fused α-aminoenones.

the crystal of compound **17** in different solvents. After many experiments, the crystalline form of **17** as yellow small needles was obtained from a mixture of 5% triethylamine in DCM in 40−70% yield. The structure was confirmed by X-ray analysis (Figure 1). To the best of our knowledge, this was the first time the crystal structure of triazoline generated in the 1,3-cycloaddition of alkyl azide and enone was obtained. These results demonstrated this transformation was efficient to construct [5,7] and [6,7] fused polycyclic α-aminoenones, which widely existed in many important polycyclic alkaloids, such as hexahydroapoerysopine (**1a**) and cephalotaxine (**1b**) (Figure 2).

Successively, our investigation of the substrate scope turned to employing nonarylchloroalkyl enones. Thus, several such substrates were synthesized and examined under the optimized condition. However, these substrates afforded none of the desired α-aminoenones, but only (Z)-*β*-aminoenones[13] (Table 2). Both cyclic and acyclic chloroalkyl enones were effective to give the *β*-aminoenones. Some important nitrogen-contained units were readily achieved in acceptable yields under this condition.

Compared with our designed strategy for α-aminoenone (Scheme 1b), it was easy to find that all nonarylchloroalkyl enone substrates gave the acyl group migration products (path a favored over path b). The regioselectivity of the migration is quite different because there are at least two factors that will control the process, namely the inherent migratory aptitude of the migrating group and stereoelectronic factors that generally present as the antiperiplannar geometry between the migrating group and the leaving group. Additionally, the stability of the newly generating positive charge at the migration origin should also be considered. For this process, the acyl group migration would develop a more stable positive charge center than that produced by aryl and alkyl group migration. From our experimental results, we thought that the migration difference between these two types of substrates might be mainly caused by the migratory aptitudes of the aryl and acyl groups. For arylchloroalkyl enone, the aryl group would migrate over the acyl group. Additionally, the preference of an antiperiplannar fashion also would be important to the regioselectivity of the 1,2-migration process. The X-ray crystallographic analysis of triazoline **17** (Figure 1) agreed well with this presumption, which showed that the dihedral angle (139.21°) of the acyl and the dinitrogen groups was closer to a straight angle than that (92.01°) between the aryl and the dinitrogen groups. However, the aryl migration took place to give α-aminoenone as the sole product. For nonarylchloroalkyl enone, the antiperiplannar migration rule and the stability of the newly formed positive charge center controlled the regioselectivity of this process, so the *β*-aminoenone formed as the major product. Currently, we are trying to obtain more crystal structures of the triazoline intermediates. We hope we can better understand the regioselectivity of the migration from these intermediates. Additionally, we are also trying to seek insight into this 1,2-migration process by means of computational chemistry in our laboratory.

By the above results, some valuable information could be obtained. First, the designed tandem [3+2] cycloaddtion/1,2-migration rearrangement reaction to α-aminoenone was feasible when arylchloroalkyl enones were employed as substrates. Second, the reaction temperature was very important for this one-pot reaction of both the arylchloroalkyl enone and nonarylchloroalkyl enone substrates. Third, this reaction showed a high sovent effect. We thought that polar aprotic solvents DMF or DMSO could well promote the fragmentation of triazoline intermediate. Last, this one-pot reaction could give some interesting aminoenones which would be valuable for the syntheses of alkaloids.

As a valuable demonstration of this strategy, a convergent synthesis of **1a**[14] (Figure 2) was undertaken due to their unique structures. As shown in Scheme 3, treatment of aminoenone **8** with acetyl chloride under basic condition gave amide **28** in 74% yield. Aldol condensation of the amide **28** finished the last ring of **1a**. Stereoselective hydrogenation of **29** delivered amide **30**, whose relative configuration was assigned by 2D-NMR. Subsequent routine reduction of lactam **30** afforded the racemic alkaloid **1a**.[15]

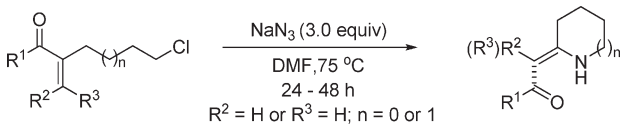
(12) We do consider that compound **14** would be in the form of a solid. We have tried to get it in the form of a solid, but failed. Fortunately the crystalline product **14** (yellow solid, mp 153−154 °C) was obtained from the solution of $CDCl_3$ in a fridge at −6 °C after NMR experiment. The analogues of **14** were all treated with the same operation in this work, unfortunately no crystallines participated. The crystallographic coordinates for **14** have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 742900. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/data_request/cif; It should be noted that the earlier assigned structure of **14** is now demonstrated to be erroneous, see: (a) Harding, T. T.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 482–485. (b) Brumfield, M. A.; Mariano, P. S.; Yoon, U. C. *Tetrahedron Lett.* **1983**, *24*, 5567–5570.

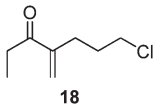
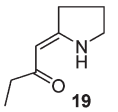
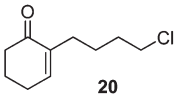
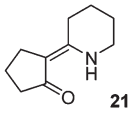
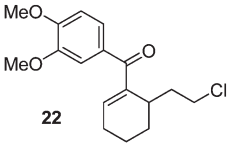
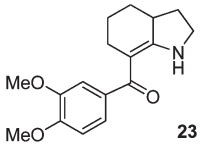
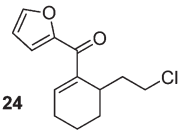
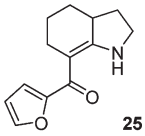
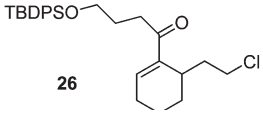
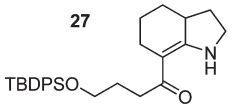
(13) The geometry was assigned based on spectroscopic, see: Gilli, P.; Bertolasi, V.; Pretto, L.; Lycka, A.; Gilli, G. *J. Am. Chem. Soc.* **2002**, *124*, 13554–13567.

(14) For the introduction of **1a**, see: (a) Prelog, V; Wiesner, K; Khorana, H. G; Kenner, G. W *Helv. Chim. Acta* **1949**, *59*, 453. (b) Warnhoff, E. W In *Molecular Rearrangements*, Part 2; de Mayo, P., Ed.; Interscience: New York, 1964; pp 846 and 847; (c) Boekelheide, V In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: London, UK, 1960; Vol. VII, pp 205. For the synthesis of **1a**, see: (d) Iida, H.; Takarai, T.; Kibayashi, C. *Chem.Commun.* **1977**, 644. (e) Iida, H.; Takarai, T.; Kibayashi, C. *J. Org. Chem.* **1978**, *43*, 975–979.

(15) Kibayashi et al. had reported the synthesis of **1a**. They only gave some typical signals of ^{1}H NMR in $CDCl_3$ with JEOL JNM-PS-100 NMR spectrometer. Our NMR spectra were obtained as solution in CD_3COCD_3, and there were slight differences with ^{1}H NMR spectra between their sample and ours in the aromatic area (6.58 vs 6.59, and 6.65 vs 6.81). For details, see ref 14e.

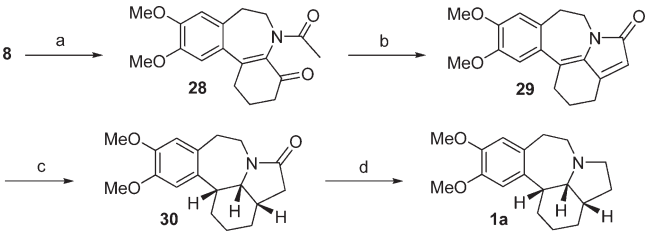
TABLE 2. One-Pot Strategy to β-Aminoenone[a]



entry	substrate	T (°C)	major product	yield[b]
1	 **18**	75	 **19**	62%
2	 **20**	75	 **21**	65%
3	 **22**	75	 **23**	74%
4	 **24**	75	 **25**	68%
5	 **26**	75	 **27**	58%

[a]Reaction condition: a mixture of chloroalkyl enone (0.2 mmol) and NaN_3 (0.6 mmol) in DMF (3 mL) was stirred at 75 °C under argon until the corresponding alkylazide enone disappeared on TLC. [b]Isolated yields.

SCHEME 3. Total Synthesis of 1a[a]



[a]Reagents and conditions: (a) 2,6-lutidine, DMAP (cat.), AcCl, THF, rt, 74%; (b) NaOMe, THF, rt, 59%; (c) $Pd(OH)_2$, H_2 (1 atm), rt, 75%; (d) $LiAlH_4$, THF, reflux, 75%.

Conclusion

In conclusion, we have realized a practically useful one-pot procedure for the syntheses of aminoenones from the chloroalkyl enone and sodium azide. During this process, the intramolecular distribution of alkylazide and enone groups was crucial for the regioselectivity of initial 1,3-dipolar cycloaddition and the conformation of intermediate triazoline also played a very important role during the 1,2-migration. Moreover, several notable aminoenones were obtained and one of them was applied to the total synthesis of hexahydroapoerysopine through simple chemical transformations. Currently, extensive applications of this methodology are underway in our laboratory.

Experimental Section

General Procedure for the Syntheses of Aminoenones. A flame-dried Schlenk flask was charged with chloroalkyl enone (0.2 mmol) and NaN_3 (0.6 mmol) in anhydrous DMF (3 mL) under argon. The mixture was heated to the appropriate temperature and stirred until the alkylazide enone disappeared (determined by TLC analysis). The mixture was then cooled to room temperature, quenched with water (note: Table 1, entries 3, 4, and 5 were quenched with 2 M HCl), stirred for 5 min, and partitioned between water and $CHCl_3$. The collected organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography on silica gel with ethyl acetate and heptanes as the eluent to give the aminoenone products.

Data for 8: R_f 0.2, 2:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86−1.92 (m, 2H), 2.37−2.41 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.94 (t, J = 7 Hz, 2H), 3.37−3.41 (m, 2H), 3.89 (s, 3H), 3.92 (s, 3H), 6.71 (s, 1H), 7.25 (s, 1H), 11.23 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.9, 29.3, 31.3, 38.6, 38.9, 55.9, 56.1, 99.6, 110.7, 111.9, 122.3, 132.2, 147.0, 150.5, 153.1, 203.7; MS (EI) m/z 273, 244, 199, 186, 57; HRMS (ESI) calcd for $C_{16}H_{20}O_3N$ (M^+ + H) 274.1438, found 274.1435; IR (neat) 1276, 1708, 2939 cm^{-1}.

Data for 10: R_f 0.4, 1:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84−1.91 (m, 2H), 2.39 (t, J = 7.6 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 2.89 (t, J = 6.4 Hz, 2H), 3.38 (s, 2H), 6.01 (s, 2H), 6.70 (s, 1H), 7.18 (s, 1H), 11.23 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.9, 30.0, 31.3, 38.5, 39.1, 101.5, 108.3, 108.6, 123.5, 133.9, 146.1, 148.9, 152.9, 204.1; MS (EI) m/z 257, 229, 228, 151, 109, 83, 71, 57; HRMS (ESI) calcd for $C_{15}H_{16}O_3N$ (M^+ + H) 258.1125, found 258.1120; IR (neat) 1027, 1566, 2918 cm^{-1}.

Data for 12. R_f 0.6, 4:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (t, J = 4.8 Hz, 2H), 2.81 (t, J = 4.6 Hz, 2H), 2.98 (t, J = 4.4 Hz, 2H), 3.48 (t, J = 4.2 Hz, 2H), 4.66 (br, 1H), 7.02 (d, J = 7.2 Hz, 1H), 7.11 (dd, J = 7.2 Hz, 1H), 7.20 (dd, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.4, 32.5, 39.2, 45.2, 125.9, 126.6, 127.2, 129.3, 130.0, 135.8, 140.9, 203.9; MS (EI) m/z 199, 198, 184, 170, 156, 141, 128, 115; HRMS (ESI) calcd for $C_{13}H_{14}ON$ (M^+ + H) 200.1070, found 200.1074.

Data for 14: R_f 0.6, 2:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.65 (m, 1H), 2.54−2.57 (m, 2H), 2.80−2.83 (m, 2H), 2.96−2.99 (m, 1H), 3.54 (t, J = 4.4 Hz, 2H), 4.63 (br, 1H), 5.96−6.01 (m, 2H), 6.63 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.8, 32.4, 38.9, 45.7, 101.2, 105.8, 110.3, 129.7, 135.7, 140.0, 146.4, 146.8, 203.6; MS (EI) m/z 242, 228, 185, 172, 159, 132, 55, 43; HRMS (ESI) calcd for $C_{14}H_{14}O_3N$ (M^+ + H) 244.0968, found 244.0972; IR (neat) 1484, 1645, 1685, 2920 cm^{-1}.

Data for 16: R_f 0.7, 1:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (t, J = 4.6 Hz, 2H), 2.86 (t, J = 4.6 Hz, 2H), 3.00 (t, J = 4.4 Hz, 2H), 3.53 (t, J = 4.2 Hz, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 4.63 (br, 1H), 6.63 (s, 1H), 6.96 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.6, 32.4, 38.9, 45.3, 55.9, 56.1, 109.5, 113.5, 128.3, 130.0, 134.4, 140.2, 147.4, 148.2, 203.4; MS (EI) m/z 259, 244, 174, 115, 77, 63; HRMS (ESI) calcd for $C_{15}H_{18}O_3N$ (M^+ + H) 260.1281, found 260.1282; IR (neat) 1504, 1690, 3354 cm^{-1}.

Data for 19: R_f 0.15, 4:1 hexane/ethyl acetate, yellow dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.6 Hz, 3H), 1.88−1.96 (m, 2H), 2.19−2.25 (m, 2H), 2.55 (t, J = 7.8 Hz, 2H), 3.51 (t, J = 7.0 Hz, 2H), 5.06 (s, 1H), 9.76 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 10.1, 21.3, 32.2, 34.6, 47.3, 88.4, 167.4, 198.8; MS (EI) m/z 139, 110, 80, 57; HRMS (ESI) calcd for $C_8H_{14}ON$ (M^+ + H) 140.1070, found 140.1070; IR (neat) 1554, 1625 cm^{-1}.

Data for 21: R_f 0.1, 4:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61−1.73 (m, 4H), 1.94−2.02 (m, 2H), 2.28 (t, J = 6.4 Hz, 4H), 2.56 (t, J = 7.8 Hz, 2H), 3.58 (t, J = 7.2 Hz, 2H), 10.57 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.1, 23.8, 26.2, 29.6, 30.9, 37.5, 47.6, 97.4, 167.2, 194.7; MS (EI) m/z 165, 164, 136, 109; HRMS (ESI) calcd for $C_{10}H_{16}ON$ (M^+ + H) 166.1226, found 166.1227; IR (neat) 1519, 1610, 2928 cm^{-1}.

Data for 23. R_f 0.1, 1:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.35 (m, 1H), 1.45−1.70 (m, 2H), 1.80−1.95 (m, 1H), 1.95−2.10 (m, 1H), 2.10−2.25 (m, 1H), 2.30−2.45 (m, 1H), 2.55−2.75 (m, 1H), 3.88 (s, 6H), 6.75−7.10 (m, 3H), 9.84 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.8, 25.7, 27.4, 30.5, 42.6, 45.9, 55.8, 97.1, 110.0, 110.6, 119.8, 135.3, 148.4, 149.4, 167.5, 192.8; MS (EI) m/z 287, 286, 165, 91; HRMS (ESI) calcd for $C_{17}H_{22}O_3N$ (M^+ + H) 288.1594, found 288.1590; IR (neat) 1261, 1512, 1613, 2931 cm^{-1}.

Data for 25: R_f 0.15, 2:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−2.10 (m, 5H), 2.25−2.45 (m, 1H), 2.50−2.75 (m, 2H), 3.15−3.35 (m, 1H), 3.45−3.62 (m, 2H), 6.43−6.45 (q, J = 1.6 Hz, 1H), 6.78−6.80 (d, J = 3.6 Hz, 1H), 7.09 (br, 1H), 7.32−7.33 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5, 30.2, 30.9, 41.9, 42.8, 45.6, 100.7, 106.6, 111.3, 138.0, 152.5, 167.6, 196.6; MS (EI) m/z 217, 177, 149, 109, 81, 43; HRMS (ESI) calcd for $C_{13}H_{16}O_2N$ (M^+ + H) 218.1176, found 218.1180; IR (neat) 1545, 1580 cm^{-1}.

Data for 27: R_f 0.3, 4:1 hexane/ethyl acetate, colorless dense oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.10−1.25 (m, 2H), 1.40−1.60 (m, 2H), 1.80−2.65 (m, 11H), 3.35−3.50 (m, 2H), 3.72 (t, J = 6.2 Hz, 2H), 7.30−7.45 (m, 6H), 7.60−7.75 (m, 4H), 9.41 (br, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2, 23.5, 23.8, 26.8, 27.5, 27.7, 30.5, 34.6, 42.3, 45.4, 63.8, 97.0, 127.5, 129.4, 134.1, 135.6, 164.4, 198.3; MS (EI) m/z 447, 390, 312, 199, 165, 123; HRMS (ESI) calcd for $C_{28}H_{38}O_2NSi$ (M^+ + H) 448.2666, found 448.2665; IR (neat) 704, 1108, 1546, 1634, 2859, 2932 cm^{-1}.

Detailed Procedure for Synthesis of the Triazoline 17. A flame-dried 5 mL Schlenk flask was charged with five-membered chloroalkyl enone **13** (0.2 mmol) and NaN_3 (0.6 mmol) in anhydrous DMF (3 mL) under argon atmosphere. The mixture was heated to 60 °C and stirred until the alkylazide enone disappeared (determined by TLC analysis), and then cooled to room temperature. The mixture was diluted with $CHCl_3$ and Et_3N (2 mmol). The organic layer was washed with cooled water three times quickly, collected, dried over $MgSO_4$, and concentrated. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel with ethyl acetate, heptanes, and Et_3N (10%, V/V) as the eluent. The crude triazoline was recrystallized with a mixture of 5% triethylamine in DCM several times, which gave pure triazoline **17** as a small yellow needle in 40−70% yield. Noteworthy was that the crystalline form of **17** began to melt at 96 °C, and completely melted at 129 °C. In the melting process, we found that the original yellow needle crystalline form of **17** was slowly changed to a milk white solid along with the release of many bubbles. ^{1}H NMR (400 MHz, CD_3COCD_3) δ 1.70−1.85 (m, 1H), 2.50−2.85 (m, 6H), 3.40−3.60 (m, 1H), 4.35−4.45 (dd, J_1 = 14 Hz, J_2 = 5.2 Hz, 1H), 5.22−5.30 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 5.92−5.95 (d, J = 1.6 Hz, 1H), 6.52 (s, 1H), 6.59 (s, 1H); ^{13}C NMR (100.6 MHz, CD_3COCD_3) δ 25.7, 28.5, 36.1, 43.6, 73.8, 89.9, 102.2, 106.7, 109.3, 126.0, 129.9, 148.1, 148.3, 206.3, 210.9; IR (neat) 1035, 1240, 1387, 1481, 1503, 1584, 1697, 1742, 2095, 2919 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}O_3N_3Na$ (M^+ + Na) 294.0849, found 294.0853.

Synthesis of 28. To a solution of the aminoenone **8** (42 mg, 0.15 mmol) in dry THF (4 mL) under argon atmosphere was added 2,6-lutidine (36 μL, 2.0 equiv), acetyl chloride (22 μL, 2.0 equiv), and DMAP (4 mg, 0.2 equiv). The resulting mixture was stirred for 40 min at room temperature. Then the mixture was quenched with 3 mL of water and partitioned between water and CH_2Cl_2. The organic layer was collected, dried over $MgSO_4$, filtered, concentrated, and chromatographed (R_f 0.1, 1:1 hexane/ethyl acetate) to afford **28** (36 mg, 74% yield, colorless dense oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90−2.20 (m, 5H), 2.25−2.50 (m, 3H), 2.90−3.10 (m, 3H), 3.80−4.00 (m, 8H), 6.69 (s, 1H), 6.98 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.1, 21.3, 27.6, 31.7, 39.2, 55.9, 56.0, 56.1, 56.2, 110.6, 111.5, 125.7, 127.4, 131.6, 146.6, 150.4, 170.0, 203.8; MS (EI) m/z 315, 287, 259, 244.

Synthesis of 29. To a solution of **28** (152 mg, 0.48 mmol) in dry THF (5 mL) under argon was added NaOMe (156 mg, 6.0 equiv). The resulting mixture was stirred for 8 h at room temperature. Then the mixture was quenched with 3 mL of water at 0°C and partitioned between water and CH_2Cl_2. The organic layer was

collected, dried over $MgSO_4$, filtered, concentrated, and chromatographed (R_f 0.1, ethyl acetate) to afford **29** (84 mg, 59% yield, colorless dense oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.02−2.10 (m, 2H), 2.80−2.90 (m, 4H), 3.07 (t, J = 7 Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 4.25 (t, J = 6 Hz, 2H), 6.49 (s, 1H), 6.78 (s, 1H), 7.20 (s, 1H); ^{13}C NMR (100.6 MHz,$CDCl_3$) δ 26.2, 28.4, 32.8, 32.9, 39.8, 55.9, 56.1, 110.2, 111.1, 112.1, 119.2, 122.4, 130.8, 137.0, 147.2, 149.7, 159.1, 162.2; IR (neat) 1507, 1651 cm^{-1}; MS (EI) m/z 297, 282, 205, 71, 57, 43; HRMS (ESI) calcd for $C_{18}H_{20}O_3N$ (M^+ + H) 298.1438, found 298.1443.

Synthesis of 30. A solution of **29** (92.7 mg, 0.312 mmol) in ethyl acetate (6 mL) was treated with $Pd(OH)_2$ (219 mg, 1.0 equiv) under hydrogen. The resulting mixture was stirred for 3 days at room temperature and then the mixture was concentrated and chromatographed (R_f 0.4, ethyl acetate) to afford **30** (70 mg, 75% yield, colorless dense oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90−1.40 (m, 4H), 1.40−1.60 (m, 1H), 1.80−2.00 (m, 1H), 2.30−3.00 (m, 7H), 3.83−3.84 (d, 6H), 4.48−4.66 (m, 2H), 6.59 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 25.2, 27.9, 28.1, 34.3, 36.6, 37.8, 45.3, 55.7, 55.9, 56.1, 109.0, 111.0, 126.7, 127.4, 147.4, 147.9, 172.4; IR (neat) 1258, 1419, 1516, 1653, 2949 cm^{-1}; MS (ESI) m/z 302 (M + H), 603 (2M + H).

Synthesis of 1a. To a solution of **30** (14 mg, 0.08 mmol) in dry THF (4 mL) under argon was added $LiAlH_4$ (6 mg, 2.0 equiv). The resulting mixture was refluxed for 30 min, and then carefully quenched with 3 mL of water and partitioned between water and CH_2Cl_2. The organic layer was collected, dried over $MgSO_4$, filtered, concentrated, and chromatographed (R_f 0.7, 100:3 ethyl acetate/Et_3N) to afford **1a** (17 mg, 75% yield, pale yellow dense oil); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.20−1.70 (m, 7H), 1.90−2.10 (m, 2H), 2.15−2.45 (m, 2H), 2.45−2.70 (m, 2H), 2.75−3.00 (m, 3H), 3.31 (s, 1H), 3.74−3.79 (d, 6H), 6.59 (s, 1H), 6.81 (s, 1H); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 22.1, 23.6, 28.5, 32.6, 40.1, 44.6, 53.8, 56.0, 56.5, 57.4, 64.4, 110.4, 112.8, 128.4, 131.0, 148.6, 148.9; IR (neat) 1517, 2919 cm^{-1}; MS (EI) m/z 287, 286, 218, 205, 191, 190, 176; HRMS (ESI) calcd for $C_{18}H_{26}O_2N$ (M^+ + H) 288.1958, found 288.1962.

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Supporting Information Available: Procedure for syntheses of substrates and characterization date for some new compounds including X-ray structures of **14** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.