JOC Article

Domino Double Michael−Claisen Cyclizations: A Powerful General Tool for Introducing Quaternary Stereocenters at C(4) of Cyclohexane-1,3-diones and Total Synthesis of Diverse Families of Sterically Congested Alkaloids

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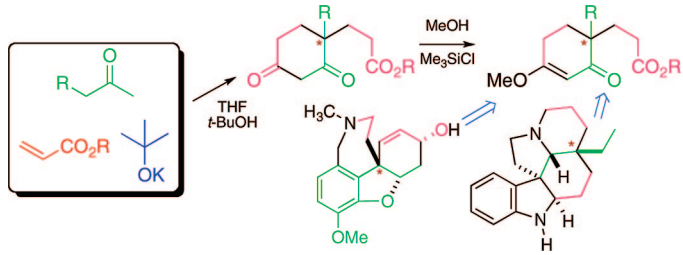

Reactions of substituted acetone derivatives with acrylic acid esters (>200 mol %) in the presence of *t*-BuOK (200 mol %) in *t*-BuOH-THF (1:1 by volume) turned out to proceed as a cascade process consisting of the first Michael addition, the second Michael addition, and the last Claisen reaction to afford 4,4-disubstituted cyclohexane-1,3-diones. Only more substituted enolates play the role of a Michael donor in this cascade process, and therefore the ketone took up two alkoxycarbonylethyl groups on the same carbon bearing more substituents. Such intermediates were followed by intramolecular Claisen reactions leading to cyclohexane-1,3-diones bearing quaternary stereogenic centers at C(4), which bears an alkoxycarbonylethyl group and the substituent of the starting acetone derivatives. Thus-obtained 4,4-disubstituted cyclohexane-1,3-diones were successfully employed for total syntheses of intricate alkaloids of biological interest such as (+)-aspidospermidine, (±)-galanthamine, (±)-lycoramine, and (±)-mesembrine, all featuring quaternary stereogenic centers. DFT calculations provided us with clear-cut explanations for the observed chemoselectivity of the cascade process involving ketone-based enolates under thermodynamically controlled conditions.

Introduction

Expeditious construction of main carbon frameworks that, at the same time, leave behind key clues for further elaboration of complex molecules should be crucial in modern organic synthesis. This may play an important role in short syntheses of natural products of biological interests. Cascade reactions have received great attention in this context.[1] We were concerned with such reactions and previously found that alkoxide-mediated domino Michael addition−Claisen reaction of simple unsymmetrical ketones with α,β-unsaturated esters can be triggered by the Michael process involving more substituted enolates as a Michael donor generated under thermodynamically controlled conditions to provide diversified cyclohexane-1,3-diones.[2] Continuing studies of this process have unveiled another hidden synthetic potential of the reaction that one more Michael process can intervene after the initial Michael process on the same site as for the initial event when the α,β-unsaturated esters was employed in an excessive amount (2−4 equiv). Thus, we referred to this process as a double Michael−Claisen reaction cascade (DMCRC) to provide an extremely efficient way to functionalized cyclohexane-1,3-diones bearing C(4)-quaternary stereogenic centers (**3**) (Scheme 1) in

(1) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCE: Weinheim, Germany, 2000; pp 39−64..

(2) Ishikawa, T.; Kadoya, R.; Arai, M.; Takahashi, H.; Kaisi, Y.; Mizuta, T.; Yoshikai, K.; Saito, S. *J. Org. Chem.* **2001**, *66*, 8000–8009.

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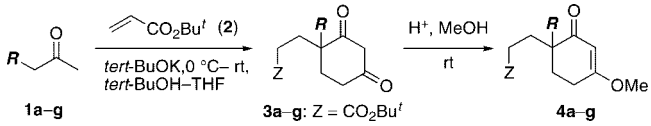
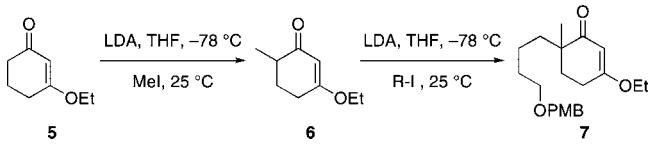
SCHEME 1. Double Michael−Claisen Reaction Cascade (DMCRC)



R: **a**: CH_3, **b**: Et, **c**: allyl, **d**: Bn, **e**: geranyl, **f**: [3,4-$(OMe)_2$]Ph, **g**: (2-OBn-3-OMe)Ph

SCHEME 2. Traditional Sequential Geminal Dialkylation of 3-Alkoxy-2-cyclohexen-1-one

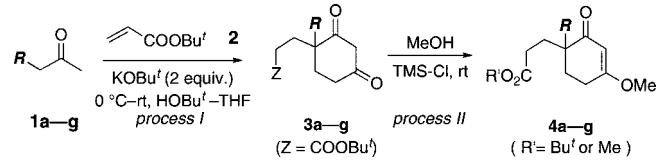


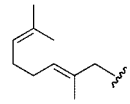
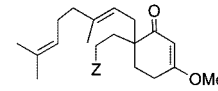
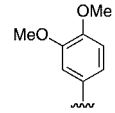
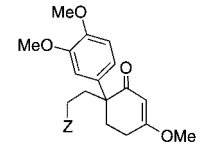
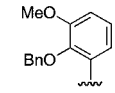
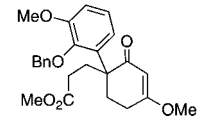
a single pot. Furthermore two carbonyl groups of **3** were highly selectively discriminated to give enol ethers (**4**) as indicated in Scheme 1. It should be noted that **4f** and **4g** bear substituted aromatic rings as one of the substituents at the C(4)-quaternary stereogenic centers, which otherwise are difficult to access.

Access to 4,4-disubstituted-1-alkoxy-1-cyclohexen-3-one frameworks such as **4** have usually relied upon traditional sequential geminal dialkylation of 3-alkoxy-2-cyclohexen-1-one (**5**).[3] For example, alkylation of kinetically generated enolates from 4-methyl-1-ethoxy-1-cyclohexen-3-one (**6**)[3c] with LDA, which can be provided through similar methylation of kinetic enolate prepared from 3-ethoxy-2-cyclohexen-1-one (**5**),[3a] leads to geminally alkylated product **7** as shown in Scheme 2. This method, however, suffers from the severe limitation that it cannot afford any aryl-substituted derivatives such as **4f** or **4g** at all.

Besides the given synthetic efficacy and substituent diversification of the DMCRC process as just mentioned, we should pay attention to the basic structural feature of **3** or **4**, which could be recognized as segments for several alkaloids of biological interest such as *Aspidosperma* alkaloid aspidospermidine (**8**),[4] *Amarillydaseae* alkaloids galanthamine (**9**)[5] or lycoramine (**10**),[6] or *Sceletium* alkaloid mesembrine (**11**),[7]

TABLE 1. Summary of DMCRC and Enol Ether Formation



R in **1**	**2**/equiv.	time/h *process I*	time/h *process II*	yield of **4**/% (based on **1**)
1a: Me	4	3	10	**4a**: 80
1b: Et	4	3	10	**4b**: 78
1c: allyl	4	3	12	**4c**: 77
1d: benzyl	4	3	12	**4d**: 70
1e: 	4	6	9	**4e**: 73 
1f: 	2.5	6	10	**4f**: 73 
1g: 	2.5	6	18	**4g**: 62 

depending on R. Indeed, concise total syntheses of all of these alkaloids from **3b**, **4g**, and **4f** have been achieved as delineating the power of DMCRC, which will be presented.

We have also conducted DFT calculations in order to gain more insight into the highly interesting chemoselectivity of this reaction. This effort gave us rational theoretical understandings why Michael reactions of ketone enolates having more substituted double bonds with α,β-unsaturated esters proceed more rapidly than those having less substituted double bonds under thermodynamically controlled conditions where such enolates are interchangeable.

Results and Discussion

DMCRC Reactions Exemplified. In Table 1 are summarized the results of DMCRC followed by discrimination of the two carbonyl groups by enol etherification. Treating substituted acetones (**1a**−**g**) with an excess amount of *t*-BuOK (2 equiv) and *tert*-butyl acrylate (**2**, 2.5−4 equiv) in THF/*t*-BuOH mixed solvent (1:1 by volume) led to **3a**−**g** in acceptable yields

(3) (a) Gannon, W. F.; House, H. O. *Org. Synth.* **1960**, *40*, 41–42. (b) Kende, A. S.; Fluzinsky, P. *Org. Synth.* **1986**, *64*, 68–69. (c) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, Y.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029. See also: (d) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7086–7090.

(4) For pioneering syntheses, see ref 18. For recent representative syntheses, see: (a) Coldman, I.; Burrell, A. J. M.; White, L. E.; Adams, H.; Oram, N. *Angew. Chem., Int. Ed* **2007**, *46*, 1–5. (b) Sharp, L. A.; Zard, S. Z. *Org Lett* **2006**, *8*, 831–834. (c) Pearson, W. H.; Aponick, A. *Org. Lett.* **2006**, *8*, 1661–1664. (d) Iyengar, R.; Schildknegt, K.; Morton, M.; Aubé, J. *J. Org. Chem.* **2005**, *70*, 10645–10652. (e) Banwell, M. G.; Lupton, D. W.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 722–737. (f) Tanino, H.; Fukunishi, K.; Ushiyama, M.; Okada, K. *Tetrahedron* **2004**, *60*, 3273–3282. (g) Marino, J. P.; Rubio, M. B.; Cao, G.; Dios, A. *J. Am. Chem. Soc.* **2002**, *124*, 13398–13399. (h) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628–4641. (i) Desmaële, D.; d′Angelo, J. *J. Org. Chem.* **1994**, *59*, 22922303. For beautiful and systematic listing of literature for the total synthesis of **8** including its racemic form, see ref 4g.

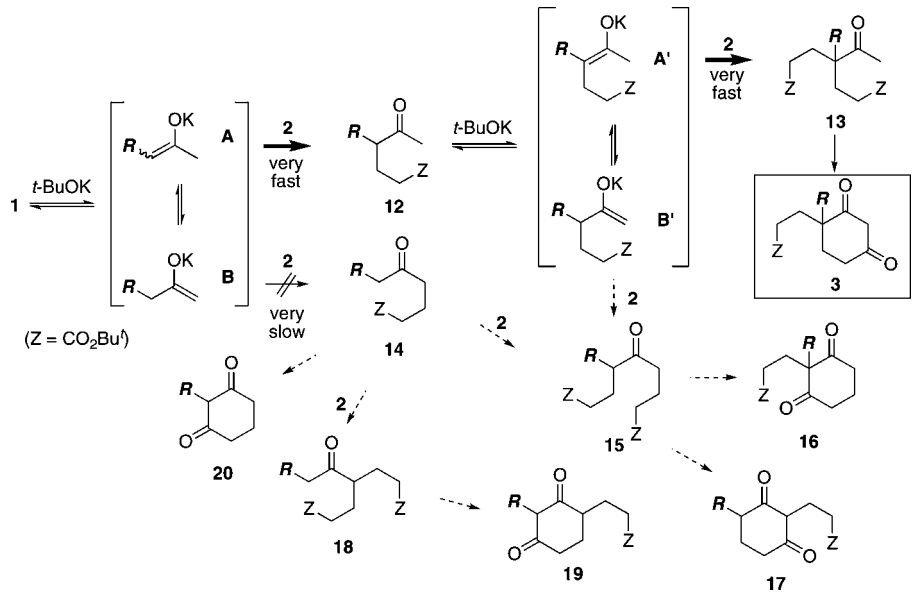
(5) For pioneering synthesis, see: (a) Barton, D. H. R.; Kirby, G. W. *Proc. Chem. Soc. London* **1960**, 392–393. For recent non-biomimetic syntheses: (b) Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. *Org. Lett.* **2006**, *8*, 1823–1825. (c) Trost, B. M.; Tang, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2795–2797. (d) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed* **2001**, *40*, 4745. For oxidative phenolic coupling: (e) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659–2661. (f) Node, M.; Kodama, S.; Hamashima, Y.; Baba, T.; Hamamichi, N.; Nishide, K. *Angew. Chem., Int. Ed.* **2001**, *43*, 3060–3062.

(6) For a recent synthesis, see: Fan, C.-A.; Tu, Y.-Q.; Song, Z.-L.; ZhangE.; Shi, L.; Wang, M.; Wang, B.; Zhang, S.-Y *Org. Lett.* **2004**, *6*, 4691–4694, and references therein.

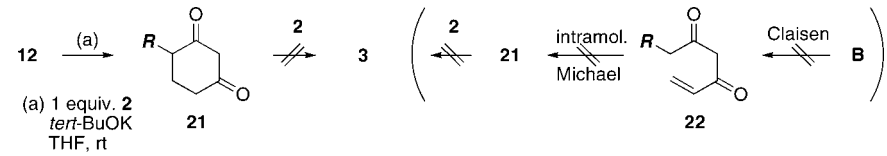
(7) For pioneering synthesis, see: (a) Shamma, M.; Rodoriquez, H. R *Tetrahedron Lett.* **1965**, *6*, 4847–4850. For recent representative synthesis, see: (b) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711–7714. (c) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143–147. (d) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747–7750. (e) Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1998**, 783–784. (f) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979–8982. (g) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263–3270. (h) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675–1686. (i) Meyers, A. I.; Hanreich, R.; Wanner, K. T *J. Am. Chem. Soc.* **1985**, *107*, 7776–7778. For a beautiful and systematic listing of literature for the total synthesis of **11**, see ref 7h.

(8) Sodium *tert*-butoxide can also effect the desired DMCRC, but sodium ethoxide gave unacceptable deteriorated product mixtures. We have also attempted amine bases such as proline, which, however, resulted in no reaction. Use of *tert*-butyl acrylate was the best choice in terms of chemical yields and suppression of side reactions. When equimolar ketones and acrylic esters were used, the DMCRC products was detected only in a trace amount in **1** for R = alkyl, allyl, or benzyl groups. On the other hand, when R was aryl groups such as **1f**,**g**, the reactions led to only DMCRC products together with the unchanged ketones recovered, and no Michael−Claisen product such as 4-arylcyclohexane-1,3-dione was detected at all.

SCHEME 3. DMCRC Mechanism



SCHEME 4. Control Experiment



(62−80%).[8] For the following enol ether formation, almost complete discrimination between the two carbonyl groups of **3** was realized for every entry under simple reaction conditions using MeOH−TMSCl to obtain **4a**−**g** in almost quantitative yields from **3**.

As the DMCRC occurs under the thermodynamically controlled conditions, we can draw the plausible mechanism as shown in Scheme 3. We should pay attention to the significant finding that the double Michael process rapidly took place at the more substituted sites of both **1** and the initial Michael products (**12**) before Claisen cyclization commenced as the final step. Only type **A** enolate reacts with **2**[9] to give **12**, which underwent the second Michael addition with **2** via type **A′** enolate affording **13**, an immediate precursor for **3** through the final Claisen reaction. Hence, we can very quickly construct quaternary centers bearing the desired substituents ***R*** even if they are aryl groups. It should be mentioned that none of **16**−**20** was obtained at all, although there is a possibility that they could be formed through routes indicated in Scheme 3.

In addition, although **12** obtained from a separate experiment (1 equiv **2**, *t*-BuOK, THF, rt) gave **21** (Scheme 4) as expected,[2] **21** did not lead to **3** by Michael reaction with **2** on treatment with the same base. Accordingly, it can definitely be concluded that **3** was furnished through an only route involving **1**, **A**, **12**, **A′**, and **13** in this order. Such a control experiment (Scheme 4) has led us to conclude that the other possible route to **3** from **B** involving initial Claisen reaction to **22** followed by intramolecular Michael reaction leading to **21** and the final intermolecular Michael reaction with **2** can completely be ruled out as indicated in brackets in Scheme 4.

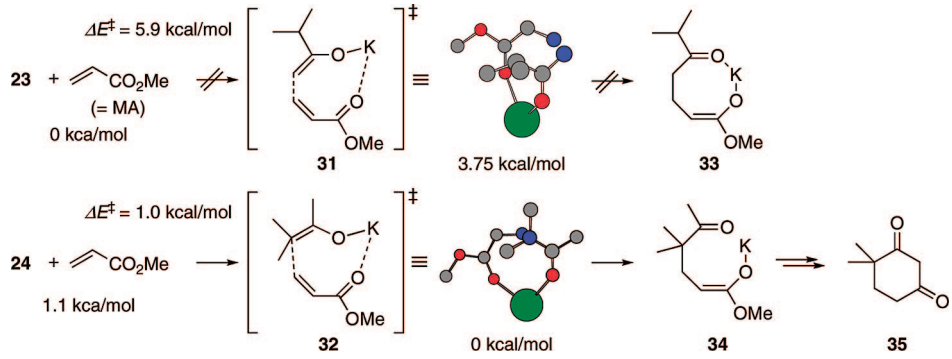
Since the type **B** enolate should exist as an equilibrium partner of the type **A** enolate under the given reaction conditions,[10] Michael reaction of **B** with **2** must have been very slow. The same thing should be true for reaction between type **B′** enolate and **2**. Since there has been a conflict of opinions with regard to the equilibrium compositions for solutions of potassium enolates derived from acyclic unsymmetrical ketones,[11] we must necessarily take kinetic aspects of Michael additions of equilibrating enolates **A** and **B** or **A′** and **B′** with **2** into account in order to rationalize the observed selectivity for the DMCRC summarized in Table 1. As the evaluation of kinetic data of this kind has not been available in the literature, we have computed the transition state energies of the reaction.

DFT Calculations for Model Enolates and Reactions. In order to diagnose enolate stability issues,[11] DFT calculations for 3-methyl-2-butanone based enolates **23** and **24** as a model were conducted using the Gaussian 03 ab initio package[12] employing B3LYP/6-31+G(d,p) as a basic function. Surprisingly enough and contrary to the textbook statements,[11a,] the more substituted enolate **24** was unequivocally less stable than less substituted enolate **23** by 3.4 kcal/mol. This is also the case for 2-butanone-based enolates **25**−**27**.[13] Although elucidation of the main factors that control such incognizant relative stability must await further studies, a stabilizing interaction between the potassium atom and the enolate double bond[14] may be more

(9) Michael reactions of acyclic or cyclic ketone enolates having a more substituted double bond with nucleophiles (Nu). Nu = ethyl or methyl acrylate: (a) Miller, J. J.; de Benneville, P. L. *J. Org. Chem.* **1957**, *22*, 1268–1269. (b) House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646–655. Nu = acrylonitrile: (c) Bruson; Hnt, A.; Riener, T. W. *J. Am. Chem. Soc.* **1942**, *64*, 2850–2858 (double cyanoethylation). (d) Barkley, L. B.; Levine, R. *J. Am. Chem. Soc.* **1950**, *72*, 3699–3701 (double cyanoethylation). (e) Bachmann, W. E.; Wick, L. B. *J. Am. Chem. Soc.* **1950**, *72*, 3388–3392. (f) Frank, R. L.; Pierle, R. C. *J. Am. Chem. Soc.* **1951**, *73*, 2341–2346. (h) Chapurlat, R.; Huet, J.; Dreux, J. *Bull. Soc. Chim. Fr.* **1967**, 2446–2450; 2450−2466.

(10) For discussion of this class, see: (a) Carey, F.; Sundberg, R. J. *Advanced Organic Chemistry, 4th ed., Part B: Reaction and Synthesis*; Kluwer Academic/Plenum: New York, 2001; pp 5−8.

SCHEME 5. Michael Reactions of Enolates 23 and 24 with Methyl Acrylate (MA)[a]



[a] Relative IRC energies for substrate-MA systems, activation energies ($\Delta E^{\ddagger}$) for each reaction, relative transition state energies for **31** and **32**, and relative energies for initial adducts (ester enolates **33** and **34**). For DFT structures, atoms in blue represent the carbons of reaction centers and larger atom in green designates potassium.

effectively involved in **23** than **24** or in **25** (**25′**) than **26** for steric reasons. The more stable nature of **26** than **27** may be attributed to a steric strain difference.

It turned out, however, that this is not a general trend. In the phenyl acetone case (**28**, **29**, and **30**), the more substituted enolates with *Z* or *E* geometry are more stable than less substituted enolate **30** and (*Z*)-isomer **28** are much more stable than the (*E*)-isomer by 8.2 kcal/mol, which is unexpectedly large and can probably be ascribed to stabilizing interaction between the potassium atom and the nearby phenyl ring (Figure 2). Further DFT studies provided a similar stabilization by an aromatic ring with conformational isomer **30** being more stable than **30′** by 3.8 kcal/mol. Thus, in order to understand the observed chemoselectivity of the DMCRC processes (Table 1), we have conducted further DFT computations including Fukui′s intrinsic reaction coordinate (IRC) protocol[16] for a Michael reaction of the above-mentioned model enolates.

The IRC energy for the **23**-MA system was calculated to be lower than that for the **24**-MA system by 1.1 kcal/mol (Scheme 5), reasonably reflecting the more stable nature of less-substituted enolate **23** (Figure 2). Nevertheless **35** was obtained exclusively from **24** as demonstrated previously.[2] This fact is given an answer by calculated transition state energies as follows. The transition states of Michael reactions could reasonably be formulated as a cyclic structure involving coordination between the two oxygen atoms and the metal center

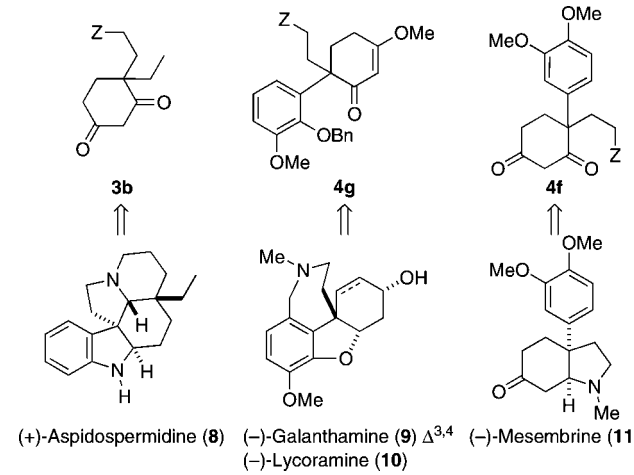


FIGURE 1. Correspondence between DMCRC products and some alkaloids in terms of both carbon backbone and heteroatom location.

such as **31** or **32**, respectively, relying on the Zimmerman−Traxler concept (Scheme 5).[15] Interestingly, **32** obtained from more substituted enolate **24** is more stable than **31** from less substituted enolate **23** by 3.75 kcal/mol, probably reflecting much larger transannular interaction exerted by an isopropyl group in **31** compared with that exerted by 1,2,2-trimethyl substituents in **32**. The following Claisen reaction leads to **35** via **34** as was clearly demonstrated previously.[17] This result provides a reason why the more substituted enolate reacts with α,β-unsaturated esters more rapidly than the corresponding less substituted enolates.

DFT calculations of the same level as that employed in the case of **23** or **24** have been carried out for other model enolates such as **25**−**30**, and the results are shown in Scheme 6. Interestingly, the IRC energy for the more substituted (*Z*)-enolate (**26**) is lower than that for the less substituted enolate (**25**) by 1.15 kcal/mol, whereas the IRC energy for the more substituted (*E*)-enolate (**27**) was higher than that for **25** by 1.92 kcal/mol. From these data, we can expect that the more substituted (*Z*)-enolate **26** would highly selectively give an adduct (**39**, thus **40**) as a precursor for 4-methylcyclohexane-1,3-dione (**41**) under thermodynamically controlled conditions including **26** as a predominant component, by which we can explain why the type-**A** enolate highly selectively led to **12** (Scheme 3). This is

(11) (a) On page 8 of ref 10: "at equilibrium the more substituted enolate is usually the dominant species. The stability of carbon-carbon double bonds increases with increasing substitution, and this effect leads to the greater stability of the more substituted enolate." (b) On page 865 of Bruice, P. Y. *Organic Chemistry*, 5th ed.; Pearson Prentice Hall: Upper Saddle River, NY, 2007: "The enolate leading to 2,2-dimethylcyclohexanone is the thermodynamic enolate ion, because it is the more stable enolate ion since it has the more substituted double bond (alkyl substitution increases enolate ion stability for the same reason it increases alkene stability)." (c) On the other hand, House and Kramar reported that less substituted enolates should be a predominant partner of equilibrium established between enolates generated from simple unsymmetrical acyclic ketones by the action of triphenylmethylpotassium in 1,2-dimethoxyethane; they analyzed deuterium distribution of recovered ketones after quenching the mixture with CH_3CO_2D/D_2O mixture. See: House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362–3379.

(12) For details of DFT calculations, see Supporting Information.

(13) For a recent ab initio study of thermodynamic stability of enolates generated from 2-butanone with methoxide anion in MeOH, see: Ikeda, H.; Yukawa, M.; Niiya, T. *Chem. Pharm. Bull.* **2006**, *54*, 731–734.

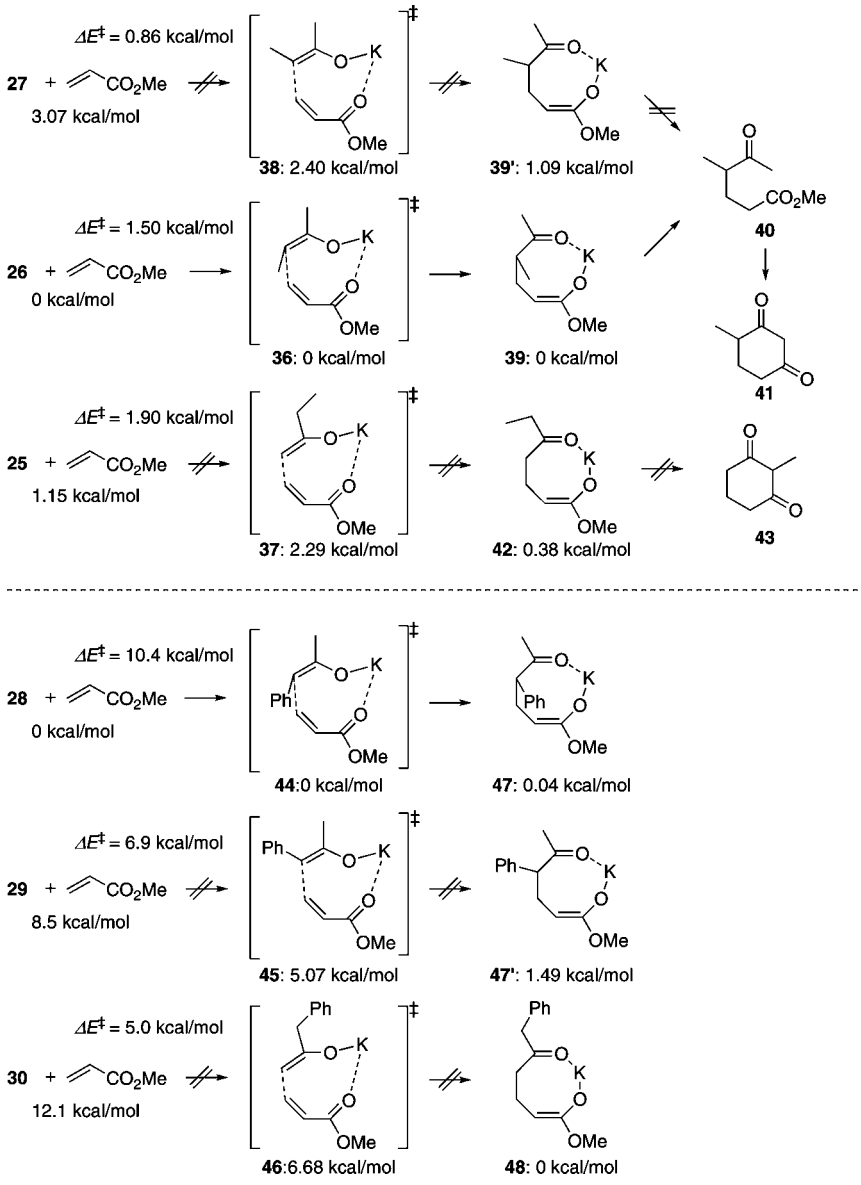
(14) Abbotto, A.; Streitwieser, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255–11268.

(15) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

(16) (a) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363–368. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–2161.

(17) See ref 2; **35** was obtained in 99% or 85% yield for *tert*-butyl or ethyl acrylate, respectively.

SCHEME 6. Michael Reactions of Enolates 25−30 with Methyl Acrylate (MA)[a]



[a] Relative IRC energies for substrate-MA systems, activation energies ($\Delta E^{\ddagger}$) for each reaction, relative transition state energies for **37**−**39** and **44**−**46**, and relative energies for initial adducts (ester enolates **39**, **39′**, **42**, **47**, **47′**, and **48**).

also consistent with the previous experiment demonstrating the exclusive formation of **41** for consecutive Michael−Claisen reaction of 2-butanone with *tert*-butyl acrylate in THF in the presence of *t*-BuOK at room temperature where no formation of **43** was observed.[2] Results for DFT calculations carried out with regard to Michael additions of phenyl acetone based enolates (**28**−**30**) with methyl acrylate clearly indicates that there would be no chance for **30** to give adduct **48** because of the highly stable nature of (*Z*)-enolate **28**, though an activation energy for Michael addition of **28** was calculated to be the highest among those obtained for these three enolates. Curtin−Hammett principle may indicate that there would exist small chance for (*E*)-enolate **29** to lead to **47′**.

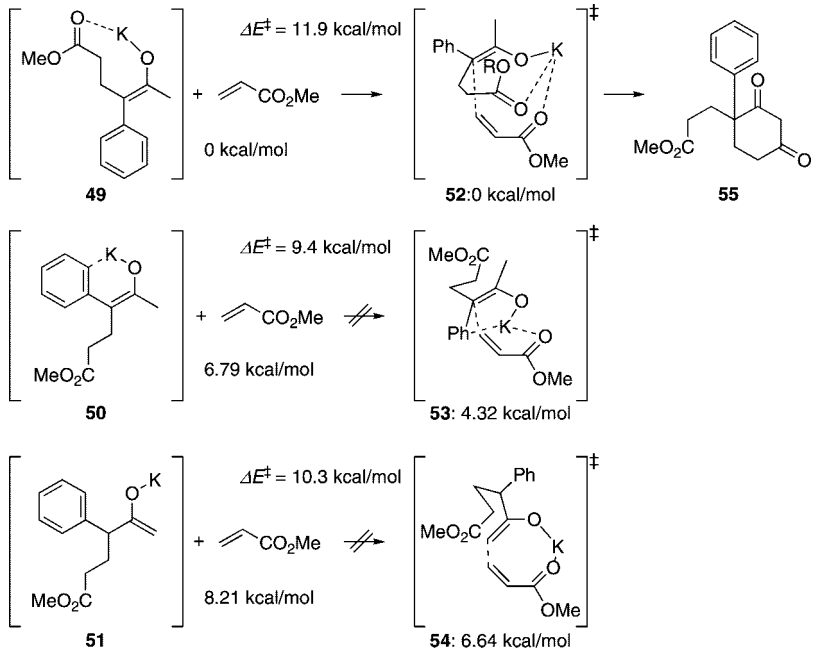
Finally, we carried out DFT calculations with regard to second Michael reactions of ketone enolates **49**, **50**, and **51**, which are convertible from **47**, **47′**, and **48**, respectively, with methyl acrylate to examine whether such hypothetical reactions proceed with very high chemoselectivity to give the expected adduct such as **55**. The results are shown in Scheme 7 and clearly suggest that the reactions should pass through a transition state such as **52** leading to **55** after the final Claisen reaction.[18] This model case can reasonably be related to the second Michael processes for real cases listed in Table 1.

To the best our knowledge, the first example of double Michael addition pertinent to the present kind was reported in 1942[9c] and demonstrated that 2-butanone reacts with an excessive amount of acrylonitrile to take up two cyanoethyl groups on the methylene carbon, giving rise to 4-acetyl-4-methylheptanedinitrile. Presumably the mechanism of this interesting chemoselective reaction is the same.

Application to the Total Synthesis of Alkaloids. Three carbon−carbon bonds can be formed in a single pot in the DMCRC process to provide cyclohexane-1,3-diones **3** having two substituents at C(4). The following enol ether formation

(18) Energy levels for the initial adducts (ester enolates) are not shown here. Reflecting the corresponding transition state structure, the ester enolates produced from **52** and **53** gave different DFT energy levels, although they lead to the same adducts after protonation. See Supporting Information for detail.

SCHEME 7. DFT Results for Michael Reactions of Hypothetical Enolates 49−51 with Methyl Acrylate (MA)[a]



[a] Relative IRC energies for substrate-MA systems, activation energies ($\Delta E^{\ddagger}$) for each reaction, and relative transition state energies for **52**−**54**.

takes place with almost complete regioselectivity leading to **4**, a 4,4-disubstituted-2-cyclohexen-1-one framework. As already mentioned above, superimposing **3** or **4** upon some alkaloids of biological interests such as **8**−**11** reveals a close correspondence of the core scaffold.

(+)-Aspidospermidine. Many *Aspidosperma* alkaloids have received considerable attention as synthetic targets because of their complex structures and potent biological activities.[19] Aspidospermidine **8** is one of the families, and development of methods for constructing its highly congested pentacyclic ring system is still attractive for synthetic chemists. Since the first synthesis of racemic aspidospermidine by Stork,[20] many syntheses and formal syntheses have been reported.[4] In Scheme 8 is illustrated the enantioselective total synthesis of (+)-aspidospermidine **8** involving the optical resolution of dione **3b**. Since optical resolution of cyclohexane-1,3-diones having C(4)-quaternary stereogenic centers has no precedent, we developed such an experimental procedure. In the event, we have found a series of practical protocol involving Lewis acid catalyzed enamine formation with optically active primary amine, separation of diastereoisomers, and final transformation of the enamine to enol ether, which should be an appropriate precursor for enone. Specifically, zinc triflate catalyzed enamine formation with (*S*)-1-phenylethylamine led to a mixture of **56a** and **56b** in very high yield.[21] The desired optically pure isomer **56a** was obtained by the combined use of recrystallization and MPLC purification,[22] and the conversion of **56a** to the known **57**[4i] was realized via a newly developed protocol consisted of *N*-methoxycarbonylation and subsequent acidic treatment in methanol.[23]

Reduction of **57** with DIBALH and subsequent mesylation of a thus-generated hydroxy group afforded chiral 4,4-disubstituted cyclohexenone (**58**), which on treatment with ethanolamine led to a bicyclic intermediate (**59**) in almost exclusive diastereoselectivity. This process may commence by Michael addition (**58** → **A** or **58** → **B**) or S_N2 reaction (**58** → **C**), the discrimination of which, however, was difficult because an attempt to isolate any of these intermediates was in vain. This result probably indicates that the following cyclization is fast, and hence intramolecular Michael reaction might be appropriate: the initial Michael addition of ethanolamine to **58** may be sluggish because of a neopentyl-type structure of the Michael acceptor. Although the mechanistic rationale of this process must await future study, it is tentatively assumed that the process involves the initial intermolecular S_N2 reaction and subsequent intramolecular Michael addition of thus-produced amine responsible for the observed very high % de as shown in Scheme 7 (**58** → **C** → **59**). Stork's ketone **60**[20] was obtained via chlorination of **59** followed by an intramolecular enolate alkylation: the optical rotation and NMR spectra of **60** were identical with those reported.[24] Transformation of **60** to (+)-aspidospermidine (**8**) was achieved after the reported procedures.[25] The present chirospecific route to **8** involves 9 steps

(19) Saxton, J. E. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, Chapter1.

(20) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2873.

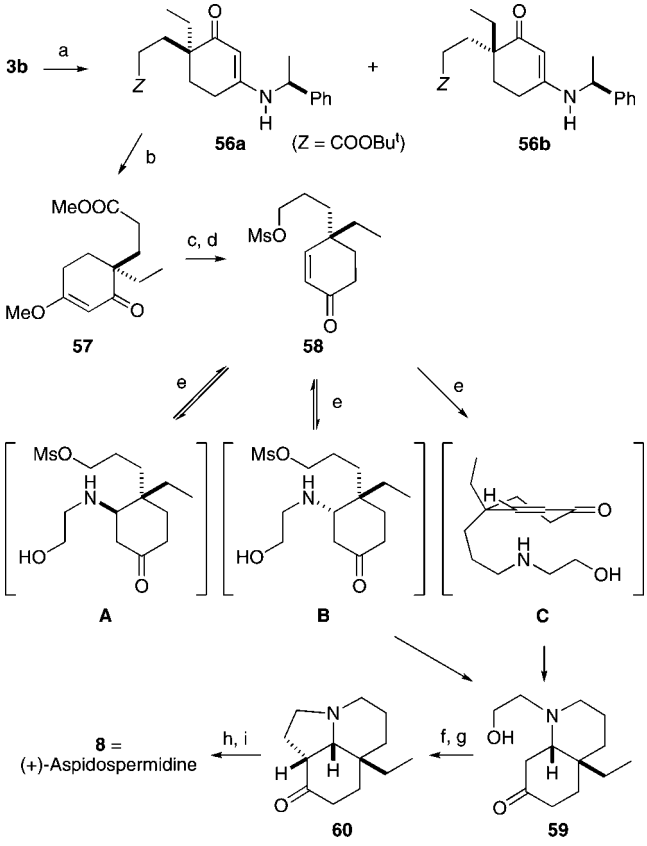
(21) An extensive survey of Lewis acid catalysts resulted in finding that $Zn(OTf)_2$ is extremely effective for this purpose. No formation of an isomer stemmed from amine attack toward another carbonyl group at C(3) was detected at all.

(22) Recrystallization afforded **56a**-rich fraction in crystals and **56b**-rich fraction as a mother liquor, the respective fraction of which led to pure **56a** and **56b** via MPLC purification.

(23) We have succeeded in transforming vinylogous amide function in **56a** to β-methoxyenone function in **57** after extensive efforts: no previous report has been found for the transformation of this kind. Optical rotation of **57** was $[\alpha]^{29}_D$ +19.7 (*c* 1.40, EtOH), which is consistent with that {$[\alpha]^{22}_D$ +19.4 (*c* 8, EtOH)} reported previously for **57**; see ref 4i.

(24) Optical rotation of **60** was $[\alpha]^{29}_D$−23.1 (*c* 0.71, $CHCl_3$), which is consistent with that {$[\alpha]^{29}_D$−24.4 (*c* 0.88, $CHCl_3$)} reported previously for **60**; see: Fukuda, Y.; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749–751.

SCHEME 8. Total Synthesis of (+)-Aspidospermidine 8[a]

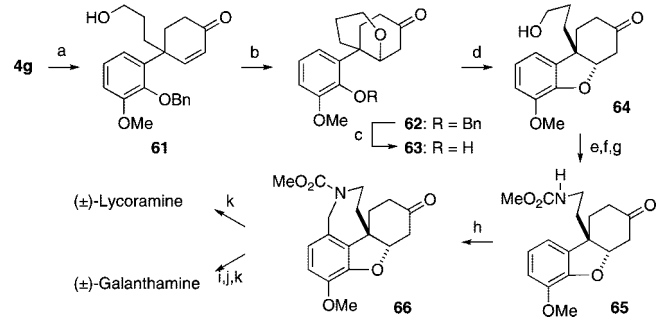


[a] Reagents and conditions: (a) 10 mol % $Zn(OTf)_2$, (*S*)-1-phenylethylamine, MeCN, 50 °C, 99%; (b) NaH, $ClCO_2Me$, THF, then MeOH−HCl, 75%; (c) DIBALH, toluene, −78 °C, 4 h; (d) MsCl, Et_3N, THF, rt, 10 h, 59% for 2 steps; (e) ethanolamine, MeOH, rt, 2 h; (f) MsCl, Et_3N, THF, rt, 20 h (g); NaH, THF, rt, 3 h, 46% for 3 steps; (h) phenylhydrazine, AcOH; (i) $NaBH_4$/EtOH, 51% for 2 steps.

with 5.2% overall yield from readily available dione **3b**, which has unequivocally proven that cascade reactions such as DMCRC process is highly profitable to short-cut synthesis of **8.** Previous chirospecific total syntheses of **8**[4g−i] required 13−22 steps.[26]

(±)-Galanthamine and (±)-Lycoramine. *Amaryllidaceae* alkaloids galanthamine (**9**) and lycoramine (**10**) have been attracting much attention of synthetic and medicinal chemists because of their biologically significant activities and their potential diversity in pharmacology. Especially, **9** has been known as a competitive and reversible inhibitor of acetylcolinesterase that enhances cognitive functions of Alzheimer's patients. Unique structural features of these alkaloids such as the tetracyclic ring system and one spiro quaternary carbon center are posing serious challenges to its practical total synthesis. The main stream of synthetic endeavors for **9** has recently shifted from venerable biomimetic oxidative phenolic couplings[5d] to nonbiomimetic approaches.[5a,c] Total synthesis of **9** or **10** presented here has been planned as a nonbiomimetic strategy and was commenced with **4g** supplied by DMCRC utilizing commercially available ketone **1g**, which is shown in Scheme 9. DIBALH reduction of **4g** afforded hydroxyenone **61**, which was treated with TsOH to promote an intramolecular oxy-Michael addition leading to the bicyclic intermediate **62**. This process played the important role of protecting the cyclic C═C bond of the enone, which otherwise could be hydrogenated

SCHEME 9. Total Synthesis of (±)-Galanthamine and (±)-Lycoramine[a]



[a] Reagents and conditions: (a) DIBALH, toluene, −78 °C, 4 h; (b) TsOH, THF, rt, 10 h; (c) Pd−C, MeOH, rt, 2 h, 65% for 3 steps; (d) $MgCl_2$, THF, 50 °C, 2 d, 82%; (e) SO_3·Py, Et_3N, DMSO, CH_2Cl_2, rt, 3 h, 74%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 80%; (g) DPPA, Et_3N, toluene−MeOH, reflux, 2 d, 80%; (h) $(CH_2O)_n$, TFA, DCE, 60 °C, 24 h, 75%; (i) TBDMSOTf, Et_3N, CH_2Cl_2, rt, 12 h; (j) $Pd(OAc)_2$, *p*-benzoquinone, MeCN, rt, 2 d, 66% for 2 steps; (k) L-Selectride, THF then LAH, THF, 50%.

under the subsequent debenzylation conditions. Thus, debenzylation was uneventfully carried out as usual to give a phenol derivative (**63**) followed by $MgCl_2$-mediated retro-Michael and a phenolic hydroxy-Michael addition process leading to the thermodynamically more stable dihydrobenzofuran **64** (82% yield) and regenerating the 3-hydroxypropyl substituent on the quaternary stereogenic center. The primary hydroxy group of **64** was oxidized to the corresponding carboxylic acid and followed by a Curtius rearrangement using Shioiri's condition[27] to afford carbamate **65**. Pictet−Spengler cyclization of **65** was effected to give the key intermediate **66**. The endgame total synthesis of (±)-galanthamine was carried out as follows: silyl enol ether formation from **66** using TBDMSOTf followed by Pd(II)-mediated oxidation[28] regioselectively furnished an enone function, which was subjected to stereoselective reduction using L-Selectride followed by carbamate to *N*-methylamine conversion with LAH. The overall yield from **1g** was 6.5% in 13 steps.[29] Stereoselective carbonyl reduction of **66** with L-Selectride followed by carbamate reduction with LAH led to (±)-lycoramine as well in overall yield of 17% for 11 steps.

(±)-Mesembrine. (−)-Mesembrine (**11**) is a member of the *Sceletium* alkaloids with potent selective serotonin reuptake inhibitory activity in the central nerves system.[30] When one of DMCRC products such as **4f** was superimposed upon **11**, we recognized that the transformation of a 2-(alkoxycarbonyl)ethyl substituent at C(4) to a 2-(*N*-methylamino)ethyl group would be the only remaining synthetic task for the construction of requisite atom framework of this natural product.

Thus, as shown in Scheme 10, ester **4f** was converted to amide **67** by ammonolysis in MeOH and followed by a Hoffman rearrangement using diacetoxyiodobenzene to afford the car-

(25) Spectroscopic data (^1H and ^{13}C NMR) of synthesized (+)-aspidospermidine were in agreement with those reported in the literature: see Supporting Information of refs 4g or 4i. Also optical rotation observed ($[\alpha]^{24}_D$ +21.1 (*c* 0.1, EtOH) was in agreement with those reported for **8** (lit.[4g] $[\alpha]^{24}_D$ +20.5 (*c* 0.6, $CHCl_3$); lit.[4i] $[\alpha]^{24}_D$ +20.8 (*c* 0.6, EtOH)).

(26) To the best of our knowledge, the shortest route to optically active aspidospermidine so far was reported by Fuji et al.: 13 steps. Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517–521.

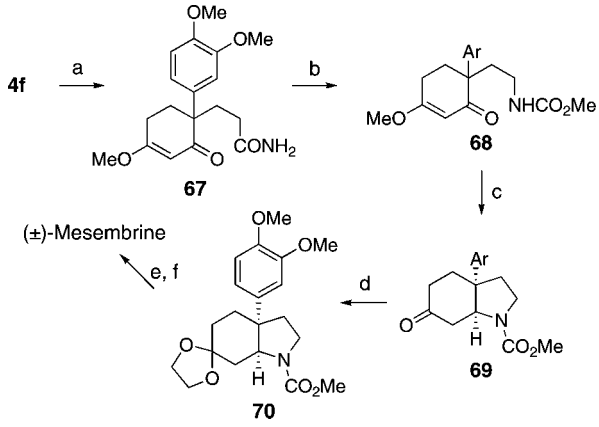
(27) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151–2157.

(28) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.

(29) Spectroscopic data (^1H and ^{13}C NMR) of synthesized racemic galanthamine were in agreement with those reported in the literature; see ref 5b.

(30) Gericke, N. P.; Van Wyk, B. E. World Patent 9746234, 1997.

SCHEME 10. Total Synthesis of (±)-Mesembrine[a]



[a] Reagents and conditions: (a) NH_3/MeOH, rt, 5 h, 81%; (b) diacetoxyiodobenzene, aqueous KOH/MeOH, 84%; (c) DIBALH/toluene, −78 °C, 4 h; 72%; (d) ethyleneglycol, *p*-TsOH/THF, rt, 10 h; (e) $LiAlH_4$/THF, rt, 3 h; (f) HCl/THF, rt, 3 h, 80% in 3 steps.

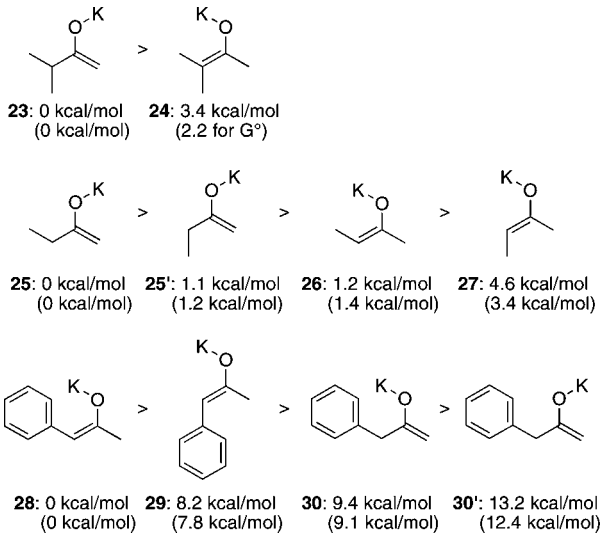


FIGURE 2. Stability orders determined by DFT calculations for some simple enolates **23**−**30** including their conformational isomers (**25′** and **30′**): total electronic energies together with Gibbs free energy indicated in parenthesis.

bamate **68** (84% yield). Converting a 1-methoxy-1-cyclohexen-3-one function in **68** to a cyclohexan-1-one function by DIBALH reduction triggered intramolecular carbamate Michael addition to afford the desired mesembrine backbone **69** in 72% yield. The endgame of this total synthesis was carried out by a series of synthetic steps involving acetalization (**70**), reduction of a carbamate moiety with $LiAlH_4$, and final acetal deprotection. The process requires 8 steps, giving a 29% overall yield from commercially available (3,4-dimethoxy)phenylacetone **1f** without any tedious or complicated experimental operations.[31]

Concluding Remarks. The pivotal Michael−Michael−Claisen cascade processes developed here provide concise, versatile, and efficient routes to 4,4-disubstituted cyclohexane-1,3-diones. Aliphatic or aromatic substituents can be introduced as one substituent at the stereogenic C(4) center. Thus, the hidden aspects of reactivity for equilibrated simple ketone-based enolates have been given privilege for building up complex molecular architectures, which at the same time gave us an opportunity to reconsider not only important basic knowledge with regard to the thermodynamic stability of ketone-based enolates but also their reactivity in Michael addition toward α,β-unsaturated esters.

4,4-Disubstituted cyclohexane-1,3-diones have significant power in the total synthesis of complex alkaloids. The 2-cyclohexen-1-one derivatives bearing a quaternary C(4)-stereogenic center available from **4a**−**f** have proven to be promising intermediates for synthesizing diverse families of alkaloids of biological interests. An optical resolution developed for the enantioselective total synthesis of (+)-aspidpspermidine suggests the potential wide applicability to other 4,4-disubstituted cyclohexane-1,3-dione derivatives. Ready availability of starting ketones[32] and operational simplicity of reactions command the strategy to other synthesis.

Experimental Section

General Procedure for the Synthesis of 3a−e and 4a−e. To a solution of **1** (10 mmol) and *tert*-butyl acrylate (5.9 mL, 40 mmol) in THF (5 mL) and *t*-BuOH (5 mL) was added potassium *tert*-butoxide (2.2 g, 20 mmol) portionwise at 0 °C. The mixture was stirred at 0 °C to room temperature for 2−3 h. The reaction was quenched by the addition of 6 N HCl (3 mL) at 0 °C and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated to give crude **3**. To a solution of the crude **3** in MeOH (15 mL) was added HCl/MeOH solution (30%, 1 mL) at room temperature. The mixture was stirred at room temperature for 1−2 h and concentrated to give an oil, which on column chromatography afforded **4** as an oil.

The following descriptions for small-scale preparation of **4f** are representative.

Methyl 3-[1-(3,4-Dimethoxy)phenyl-4-methoxy-2-oxocyclohex-3-en-1-yl]propanoate (4f). To a solution of **1f** (338 mg, 1.74 mmol) in THF (2 mL) was added *t*-BuOH (2 mL) and *tert*-butyl acrylate (0.57 mL, 3.0 equiv), followed by the addition of potassium *tert*-butoxide (0.039 g, 1.3 equiv) at 0 °C. The mixture was stirred at room temperature for 4 h. The reaction was quenched with 6 N HCl at 0 °C, dried over Na_2SO_4, and concentrated to give a crude mixture. To a solution of the crude mixture in MeOH (5 mL) was added HCl/MeOH solution (30%, 0.5 mL) at 0 °C. The mixture was stirred at room temperature for 12 h, quenched by the addition of Et_3N at 0 °C, and concentrated by a rotary evaporator to give an oil, which on column chromatography afforded **4f** (436 mg, 73%) as a yellow oil: ^{1}H NMR δ 2.45−2.02 (m, 8H), 3.59 (s, 3H), 3.61 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 5.37 (s, 1H), 6.81−6.75 (m, 3H); ^{13}C NMR δ 200.4, 176.6, 173.8 148.8, 147.8, 131.7, 118.8, 111.0, 110.6, 102.1, 56.0, 55.9, 55.7, 51.4, 51.2, 34.8, 31.3, 30.1, 26.5; IR (film) 1736, 1612 cm^{-1}; R_f = 0.33 (hexane/EtOAc = 1:1); HRMS (EI), *m*/*z* 348.1560 (calcd for $C_{19}H_{24}O_6$ *m*/*z* 348.1573). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.32; H, 6.96.

Total Synthesis of (+)-Aspidospermidine (8). *tert*-Butyl 3-{(1*S*)-1-Ethyl-4-[(*S*)-1-phenylethyl]amino-2-oxocyclohex-3-en-1-yl}propanoate (56a) and *tert*-Butyl 3-{(1*R*)-1-Ethyl-4-[(*S*)-1-phenylethyl]amino-2-oxocyclohex-3-en-1-yl}propanoate (56b). To a solution of **3b** (3.11 g 11.5 mol) and (*S*)-(−)-1-phenylethylamine (1.637 mL, 1.15 mmol, 1.1 equiv) in acetonitrile (50 mL) was added $Zn(OTf)_2$ (418 mg, 1.15 mmol, 10 mol %) at room temperature. The mixture was stirred at 60 °C for 3 h and concentrated to give a yellow oil, which on column chromatography afforded a mixture of **56a** and **56b** (4.21 g, 99%) as a colorless solid. Recrystallization of the mixture from EtOH/hexane (1:3) mixed solvent (4 °C, 12 h) gave solids (**56a** rich, 6:1) and filtrates (**56b** rich, 6:1). Subsequent preparative HPLC purification of thus-

(31) Spectroscopic data (^{1}H and ^{13}C NMR) of synthesized racemic mesembrine were in agreement with those reported in the literature; see refs 7c and 7h.

(32) Ketones **1a**−**f** are commercial products.

obtained two parts was successful in complete separation between **56a** and **56b**; hexane/EtOAc = 3/1, pressure = 10 kg/cm^2, 300 mm × 26 mm column packed with 40 g of SiO_2 with a particle size of 40 μm. The combined weight of pure **56a** or **56b** as a colorless gum was 2.10 g for each. **56a**: ^{1}H NMR δ 0.82 (t, 3H, J = 7.4 Hz), 1.41 (s, 9H), 1.48 (d, 3H, J = 6.9 Hz), 1.48−1.90 (m, 6H), 2.10−2.20 (m, 2H), 2.40 (t, 2H, J = 6.3 Hz), 4.44−4.51 (m, 1H), 4.92 (s, 1H), 5.02−5.20 (br, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR δ 200.3, 173.5, 161.1, 142.8, 128.8, 127.4, 125.7, 97.9, 80.0, 52.7, 44.9, 30.5, 29.8, 29.4, 28.1, 27.8, 26.0, 23.2, 8.3; IR (film) 2978, 1720, 1581, 1539 cm^{-1}; R_f = 0.46 (hexane/EtOAc = 1:1); HRMS (EI), m/z 371.2444 (Calcd for $C_{23}H_{33}NO_3$ m/z 371.2460). **56b**: ^{1}H NMR δ 0.79 (t, 3H, J = 15.0 Hz), 1.41 (s, 9H), 1.39−1.60 (m, 2H), 1.47 (d, 3H, J = 7.7 Hz), 1.70−1.90 (m, 4H), 2.14−2.50 (m, 4H), 4.41−4.54 (m, 1H), 4.96−5.00 (br, 2H), 7.20−7.38 (m, 6H); ^{13}C NMR δ 200.2, 173.6, 161.3, 142.8, 128.8, 127.5, 125.7, 97.9, 80.0, 52.8, 44.9, 30.5, 29.7, 29.4, 28.1, 27.6, 26.0, 23.3, 8.3. IR (film) 2978, 1720, 1581, 1539 cm^{-1}; R_f = 0.40 (hexane/EtOAc = 1:1); HRMS (EI), m/z 371.2470 (Calcd for $C_{23}H_{33}NO_3$ m/z 371.2460).

Methyl (+)-3-[(1*S*)-1-Ethyl-4-methoxy-2-oxocyclohex-3-en-1-yl]propanoate (57). To a solution of **56a** (1.55 g, 4.17 mmol) in CH_2Cl_2 (10 mL) was added NaH (501 mg, 12.5 mmol, 3 equiv) at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To this mixture was added ethyl chloroformate (1.20 mL, 12.6 mmol, 3 equiv) at 0 °C, and the resulting mixture was stirred at room temperature for 22 h. The reaction was quenched by the addition of H_2O and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give a crude oil. To a solution of the crude oil in MeOH (15 mL) was added HCl/MeOH solution (30%, 1 mL) at room temperature. The mixture was stirred at 60 °C for 16 h, quenched by the addition of saturated aqueous solution of $NaHCO_3$ (5 mL) at 0 °C, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give a crude oil, which on column chromatography afforded **57** as a pale yellow oil (753 mg, 75%): $[\alpha]^{21}_D$ +19.7 (*c* 1.4, EtOH) [lit.[4i] $[\alpha]^{21}_D$ +19.4 (*c* 1.4, EtOH)]; ^{1}H NMR δ 0.83 (t, 3H, J = 7.5 Hz), 1.54 (dq, 2H, J = 7.5, 12.1 Hz), 1.72−1.96 (m, 4H), 2.27 (dt, 2H, J = 6.1, 9.8 Hz), 2.43 (t, 2H, J = 7.6 Hz), 3.64 (s, 3H), 3.66 (s, 3H), 5.25 (s, 1H); ^{13}C NMR δ 202.5, 176.3, 174.3, 101.4, 55.6, 51.6, 45.9, 29.1, 29.0, 28.9, 27.0, 25.4, 8.1 (NMR data are fully consistent with those reported in the literature just mentioned above); IR (film) 2943, 1736, 1651, 1612 cm^{-1}; R_f = 0.57 (hexane/EtOAc = 1:1); HRMS (EI), m/z 240.1368 (calcd for $C_{13}H_{20}O_4$ m/z 240.1362). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.11; H, 8.37.

3-[(1*R*)-1-Ethyl-4-oxocyclohex-2-en-1-yl]propyl methanesulfonate (58). To a solution of **57** (447 mg, 1.86 mmol) in 22 mL of toluene was added DIBALH in toluene (11.3 mL, 11.9 mmol, 6.0 equiv) at −78 °C. The mixture was stirred at −78 °C to room temperature for 18 h. The reaction was quenched by the addition of water at 0 °C, filtered through a celite pad, and concentrated to give a crude oil. To a solution of the crude oil in THF (20 mL) was added Et_3N (0.59 mL, 3.7 mmol, 2.0 equiv), followed by the addition of methanesulfonyl chloride (0.190 mL, 2.79 mmol, 1.5 equiv) at 0 °C. The mixture was stirred at 0 °C for 30 min and concentrated to give an oil, which on column chromatography afforded **58** as a brown oil (285 mg, 59%): ^{1}H NMR δ 0.88 (t, 3H, J = 7.7 Hz), 1.42−1.60 (m, 4H), 1.68−1.80 (m, 2H), 1.81−1.90 (m, 2H), 2.39−2.44 (m, 1H), 2.99 (s, 3H), 4.21 (t, 2H, J = 6.3 Hz), 5.92 (d, 1H, J = 10.2 Hz), 6.65 (d, 1H, J = 10.2); ^{13}C NMR δ 199.2, 157.5, 128.5, 69.9, 37.8, 37.3, 33.7, 32.9, 30.3, 30.1, 24.0, 8.2; IR (film) 2982, 1674, 1350 cm^{-1}; R_f = 0.40 (hexane/EtOAc = 1:1); HRMS (EI), m/z 260.1079 (calcd for $C_{12}H_{20}O_4S$ m/z 260.1082).

(6aR,9aS,9bS)-6a-Ethyldecahydropropyrrolo[3,2,1-*ij*]quinolin-9-one (60). To a solution of **58** (267 mg, 1.02 mmol) in EtOH (10 mL) was added 2-aminoethanol (0.12 mL, 2.1 mmol, 2 equiv) at room temperature. The mixture was stirred at room temperature for 20 h, quenched with 2 N KOH (1 mL) at 0 °C, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give **59** as a crude oil. To a solution of the crude **59** in THF (5 mL) was added Et_3N (0.70 mL, 4.4 mmol, 4 equiv), followed by the addition of methanesulfonyl chloride (0.23 mL, 3.3 mmol, 3 equiv) at 0 °C. The mixture was stirred at room temperature for 20 h, quenched by the addition of water, and extracted with EtOAc. The combined extracts were concentrated to give an oil, which was dissolved in THF (5 mL), and to the thus-obtained solution was added NaH (60% in oil, 132 mg, 3.3 mmol, 3 equiv) at 0 °C. The mixture was stirred at room temperature for 3 h, quenched with NH_4Cl at 0 °C, and concentrated to give an oil, which on column chromatography afforded **60** as a colorless oil (98 mg, 46%): $[\alpha]^{29}_D$ −23.1 (*c* 0.71, $CHCl_3$) {lit.[24] $[\alpha]^{29}_D$ −24.4 (*c* 0.88, $CHCl_3$)}; ^{1}H NMR δ 0.93 (t, 3H, J = 7.6 Hz), 1.03−1.16 (m, 1H), 1.24−1.38 (m, 1H), 1.44−1.57 (m, 2H), 1.57−1.98 (m, 7H), 2.19−2.48 (m, 4H), 2.67 (ddd, 1H, J = 2.1, 5.1, 8.7 Hz), 2.97−3.06 (m, 2H); ^{13}C NMR δ 211.1, 73.4, 53.1, 52.8, 48.0, 36.7, 34.6, 32.7, 30.0, 26.0, 21.19, 21.15, 7.0 (NMR data are fully consistent with those reported in the literature just mentioned above for the optical rotation); IR (film) 2935, 2725, 1709 cm^{-1}; R_f = 0.38 (hexane/EtOAc = 3:1); HRMS (EI), m/z 207.1619 (calcd for $C_{13}H_{21}NO$ m/z 207.1623). Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.18; H, 10.16; N, 6.80.

(+)-Aspidospermidine (8). To a solution of **60** (130 mg, 0.63 mmol) in AcOH (6 mL) was added phenylhydrazine (0.093 mL, 0.95 mmol, 1.5 equiv) at room temperature. The mixture was stirred at 95 °C for 9 h, quenched by the addition of 15% aqueous NaOH solution, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4, concentrated, and passed through a short column of Al_2O_3 using AcOEt to give dehydroaspidospermidine as a yellow oil (127 mg, 71%). To a solution of dehydroaspidospermidine (70 mg 0.25 mmol) in MeOH (3 mL) was added $NaBH_4$ (47 mg 1.25 mmol, 5 equiv) at 0 °C, and the mixture was stirred at 0 °C to room temperature for 2 h, quenched with water, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to obtain an oil, which was purified by column chromatography to furnish (+)-**8** (51 mg, 72%); $[\alpha]^{29}_D$ +21.1 (*c* 0.50, EtOH) {lit.[4g] $[\alpha]^{24}_D$ +20.5 (*c* 0.6, $CHCl_3$); lit.[4i] $[\alpha]^{20}_D$ +20.8 (*c* 0.6, EtOH)}; ^{1}H NMR δ 0.63 (t, 3H, J = 7.7 Hz), 0.79−0.94 (m, 1H), 1.01−1.20 (m, 2H), 1.23−1.58 (m, 4H), 1.58−1.82 (m, 3H), 1.87−2.03 (m, 2H), 2.17−2.38 (m, 3H), 2.99−3.20 (m, 3H), 3.52 (dd, 1H, J = 6.4, 11.2 Hz), 6.62 (d, 1H, J = 7.7 Hz), 6.74 (t, 1H, J = 7.3 Hz), 7.02 (dt, 1H, J = 7.3, 7.7 Hz), 7.08 (d, 1H, J = 7.3 Hz); ^{13}C NMR δ 149.4, 135.6, 127.0, 122.7, 118.9, 110.3, 71.2, 65.5, 53.8, 53.3, 52.9, 38.7, 35.6, 34.4, 29.9, 28.0, 23.0, 21.7, 6.7 (NMR data are also fully consistent with those reported in the literature[4g,i]); IR (film) 3363, 2931, 2785, 1604 cm^{-1}; R_f = 0.23 (hexane/EtOAc = 1:1); HRMS (EI), m/z 282.2093 (calcd for $C_{19}H_{26}N_2$ m/z 282.2096).

Total Synthesis of (±)-Galanthamine [(±)-9]. 4a-(2-Benzyloxy-3-methoxy)phenyloctahydrochromen-7-one (62). To a solution of **4g** (337 mg, 0.79 mmol) in toluene (5 mL) was added DIBALH in toluene (4.0 mL, 4.0 mmol) at −78 °C. The mixture was stirred at −78 °C for 4 h. The reaction was quenched by the addition of water at 0 °C, filtered through a celite pad, and concentrated to give an oil, which was briefly purified by passing through a short silica gel column to afford crude 4,4-disubstituted cyclohex-2-en-1-one (**61**). To a solution of **61** in THF (5 mL) was added $TsOH\cdot H_2O$ (30 mg, 0.16 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h, quenched with saturated aqueous $NaHCO_3$ at 0 °C, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography to obtain **62** as a yellow oil (198 mg, 68%): ^{1}H NMR δ 1.25−1.35 (m, 1H), 1.73−1.86 (m, 1H), 1.87−2.00 (m, 1H), 2.00−2.19 (m, 1H), 2.25−2.60 (m, 5H), 2.84 (td, 1H, J = 14.0, 4.7 Hz) 3.19 (br t, 1H, J = 11.3 Hz), 3.90 (s, 3H), 3.92−3.99 (m, 1H), 4.92 (br s, 1H), 5.03 and 5.22 (ABq, 2H, J = 11.3 Hz), 6.93 (dd, 1H, J = 8.2, 2.2

Hz), 7.06 (dd, 1H, J = 7.4, 2.2 Hz), 7.11 (t, 1H, J = 8.2, 7.4 Hz), 7.32−7.53 (m, 5H); ^{13}C NMR δ 209.9, 153.6, 147.2, 137.4, 137.0, 128.4 (2C), 127.9, 124.0, 119.5, 111.2, 79.2, 74.5, 68.4, 55.7, 44.9, 42.1, 38.2, 34.9, 26.8, 21.9; IR (film) 2956, 1720, 1577, 1462, 1263.1 cm^{-1}; R_f = 0.40 (hexane/EtOAc = 2:1); HRMS (EI), *m/z* 366.1829 (calcd for $C_{23}H_{26}O_4$ *m/z* 366.1831). Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15. Found: C, 75.09; H, 7.17.

4a-(2-Hydroxy-3-methoxy)phenyloctahydrochromen-7-one (63). A suspension of Pd/carbon (5%, 41 mg) in MeOH (1.5 mL) was stirred at room temperature for 2 h under H_2 atmosphere. To this mixture was added a solution of **62** (110 mg, 0.30 mmol) in MeOH (1.5 mL) at room temperature, and the resulting mixture was stirred at room temperature for 4 h under H_2, filtered through a celite pad, and concentrated to obtain a crude solid, which was purified by column chromatography to afford **63** as a colorless amorphous solid (83 mg, 100%): ^{1}H NMR δ 1.37−1.47 (m, 1H), 1.77−1.88 (m, 1H), 1.90−2.08 (m, 1H), 2.19 (dt, 1H, J = 13.1, 4.7 Hz), 2.30−2.44 (m, 4H) 2.50 (dt, 1H, J = 15.1, 3.3 Hz) 2.80−2.93 (m, 1H) 3.59 (ddd, 1H, J = 11.3, 3.0, 2.7 Hz) 4.07 (ddt, 1H, J = 11.3, 5.2, 1.4 Hz) 5.03 (brs, 1H), 6.34 (s, 1H), 6.82 (dd, 1H, J = 1.7, 8.0 Hz), 6.87 (t, 1H, J = 8.0 Hz), 7.00 (dd, 1H, J = 8.0, 1.7 Hz); ^{13}C NMR δ 210.3, 147.1, 144.3, 129.1, 119.7 (2C), 108.9, 79.1, 68.8, 56.1, 45.0, 41.6, 38.2, 33.3, 26.5, 22.0; IR (film) 3338, 2956, 1713, 1585, 1255 cm^{-1}; R_f = 0.40 (hexane/EtOAc = 2:1); HRMS (EI), *m/z* 276.1355 (calcd for $C_{16}H_{20}O_4$ *m/z* 276.1362).

9b-(3-Hydroxypropyl)-6-methoxy-1,4,4a,9b-tetrahydro-2*H*-dibenzofuran-3-one (64). To a solution of **63** (627 mg, 2.27 mmol) in THF (10 mL) was added $MgCl_2$ (1.03 g, 5.67 mmol) at room temperature, and the resulting mixture was stirred at 50 °C for 2 d. The reaction was quenched by the addition of H_2O at 0 °C and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which on column chromatography afforded **64** as a colorless oil (535 mg, 85%): ^{1}H NMR δ 1.35−1.50 (m, 1H), 1.58−1.73 (m, 1H), 1.75−2.05 (m, 5H), 2.24−2.29 (m, 1H), 2.67 (dd, 1H, J = 17.3, 3.6 Hz), 2.96 (dd, 1H, J = 17.3, 3.0 Hz), 3.64 (t, 1H, J = 6.3, 6.1 Hz), 3.85 (s, 3 H), 4.95 (t, 1H, J = 3.3, 3.0 Hz), 6.72 (d, 1H, J = 7.4 Hz), 6.76 (d, 1H, J = 7.1 Hz), 6.88 (t, 1H, J = 7.4, 7.1 Hz); ^{13}C NMR δ 209.3, 147.7, 144.3, 132.7, 121.9, 115.4, 111.4, 85.2, 62.7, 55.8, 48.0, 41.8 (2C), 35.9, 32.8, 27.5; IR (KBr disk) 3423, 2941, 1716, 1619, 1459, 1284 cm^{-1}; R_f = 0.10 (hexane/EtOAc = 1:1); HRMS (EI), *m/z* 276.1366 (calcd for $C_{16}H_{20}O_4$ *m/z* 276.1362). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.34; H, 7.27.

1,2,4a,9b-Tetrahydro-6-methoxy-9b-[3-(*N*-methoxycarbonylamino)ethyldibenzofuran-3-one (65). To a solution of **64** (351 mg, 1.27 mmol) in DMSO (3 mL) and CH_2Cl_2 (3 mL) were added SO_3·Py (810 mg, 5.09 mmol) and Et_3N (1.30 mL, 9.33 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h, quenched by the addition of saturated aqueous NH_4Cl at 0 °C, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which, on column chromatography, afforded an aldehyde as a yellow oil (279 mg, 80%): ^{1}H NMR δ 1.90−2.05 (m, 4H), 2.05−2.42 (m, 2H), 2.4−2.59 (m, 1H), 2.67 (dd, 1H, J = 17.0, 3.6 Hz), 2.94 (dd, 1H, J = 17.0, 3.3 Hz), 3.86 (s, 3H), 4.88 (t, 1H, J = 3.6 Hz), 6.68 (d, 1H, J = 7.7 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.90 (t, 1H, J = 8.0, 7.7 Hz), 9.73 (s, 1H); ^{13}C NMR δ 208.6, 200.8, 147.6, 144.4, 131.3, 122.2, 115.1, 111.7, 84.8, 55.8, 47.7, 41.6, 39.3, 35.7, 33.0, 30.8; IR (film) 2937, 1720, 1618, 1492.6, 1284 cm^{-1}; R_f = 0.4 (hexane/EtOAc = 1:1).

To a solution of the aldehyde (285 mg, 1.03 mmol) in *tert*-butanol (4 mL) and H_2O (1 mL) were added 2-methyl-2-butene (1.05 mL, 2.10 mmol), $NaClO_2$ (280 mg, 3.10 mmol), and NaH_2PO_4 (250 mg, 1.60 mmol) at 0 °C. The mixture was stirred at room temperature for 5 h and concentrated to obtain a yellow oil, which was purified by column chromatography to afford a carboxylic acid (276 mg, 91%) as a colorless crystals: ^{1}H NMR δ 1.92−2.09 (m, 3 H), 2.16−2.46 (m, 5 H), 2.66 (dd, 1H, J = 17.0, 3.3 Hz), 2.94 (dd, 1H, J = 17.0, 3.0 Hz), 3.84 (s, 3H), 4.90 (t, 1H, J = 3.3 Hz), 6.72 (d, 1H, J = 7.4 Hz), 6.76 (d, 1H, J = 7.1 Hz), 6.88 (dd, 1H, J = 7.4, 7.1 Hz); ^{13}C NMR d 209.0, 178.7, 147.6, 144.4, 131.2, 122.2, 115.2, 111.8, 84.7, 55.8, 47.8, 41.6, 35.7, 33.9, 32.8, 29.5; IR (KBr disk) 3580, 2870, 1720, 1619, 1492, 1282 cm^{-1}; R_f = 0.3 (EtOAc).

To a solution of the carboxylic acid (350 mg, 1.21 mmol) in toluene (5 mL) were added diphenylphosphoryl azide (0.3 mL, 1.36 mmol) and Et_3N (0.84 mL, 6.03 mmol) at room temperature, and the resulting mixture was heated under reflux for 30 min, when MeOH (5 mL) was added to the mixture. The mixture was stirred at that temperature for 12 h, quenched with saturated aqueous $NaHCO_3$ at 0 °C, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which was purified by column chromatography to afford **65** as a yellow oil (308 mg, 80%): ^{1}H NMR δ 1.80−2.10 (m, 5H), 2.15−2.24 (m, 1H), 2.63 (dd, 1H, J = 17.0, 3.6 Hz), 2.95 (dd, 1H, J = 17.0, 3.3 Hz), 2.93−3.10 (m, 1H), 3.10−3.35 (m, 1H), 3.56 (s, 3H), 3.78 (s, 3H), 4.90−5.05 (br, 2H), 6.74 (d, 1H, J = 7.7 Hz), 6.76 (d, 1H, J = 7.7 Hz), 6.85 (t, 1H, J = 7.7 Hz); ^{13}CNMR δ 208.8, 156.8, 147.2, 144.2, 131.5, 121.9, 115.2, 111.5, 84.9, 55.6, 51.8, 47.0, 41.5, 39.2, 36.9, 35.5, 32.5; IR (film) 3361, 1716, 1619, 1531, 1268 cm^{-1}; R_f = 0.5 (EtOAc); HRMS (EI), *m/z* 319.1427 (calcd for $C_{17}H_{21}NO_5$ *m/z* 319.1420).

1,2-Dihydro-(*N*-methoxycarbonyl)narwedine (66). To a solution of **65** (109 mg, 0.34 mmol) in 1,2-dichloroethane (10 mL) were added *p*-formaldehyde (50 mg, 1.7 mmol) and TFA (0.27 mL, 3.5 mmol) at room temperature. The mixture was stirred at 50 °C for 8 h, quenched with saturated aqueous $NaHCO_3$ at 0 °C, and extracted with EtOAc. The combined extracts was dried over Na_2SO_4 and concentrated to give an oil, which on column chromatography afforded **66** as a colorless oil (113 mg, 100%): ^{1}H NMR δ 1.74−1.90 (m, 2H), 1.90−2.12 (m, 2H), 2.23−2.36 (m, 2H), 2.61 (dd, 1H, J = 17.6, 2.8 Hz), 2.96 (dd, 1H, J = 17.6, 3.3 Hz), 3.16−3.36 (br, 1H), 3.61 (s, 3H), 3.79 (s, 3H), 4.00−4.44 (m, 2H), 4.69 (t, 1H, J = 3.3 Hz), 4.65−4.93 (br, 1H), 6.63−6.71 (m, 2H); ^{13}C NMR δ 207.9, 155.9, 147.5, 144.0, 131.3, 129.2, 121.2, 111.6, 88.0, 56.0, 52.5, 50.7, 47.6, 45.8, 39.9, 39.0, 35.4, 30.0; IR (neat) 2959, 1722, 1699, 1625, 1263 cm^{-1}; R_f = 0.4 (EtOAc); HRMS (EI), *m/z* 331.1415 (calcd for $C_{18}H_{21}NO_5$ *m/z* 331.1420). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.19; H, 6.43; N, 4.20.

(±)-Galanthamine [(±)-9]. To a solution of **66** (238 mg, 0.71 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (0.30 mL, 2.15 mmol) and *tert*-butyldimethylsilyl triflate (0.33 mL, 1.44 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h, quenched with saturated aqueous NH_4Cl at 0 °C, and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated to give an oil, which on column chromatography afforded an enol silyl ether as a yellow oil (288 mg, 100%). To a solution of this enol silyl ether (288 mg, 0.71 mmol) in CH_3CN (4 mL) were added $Pd(OAc)_2$ (240 mg, 1.07 mmol) and *p*-benzoquinone (116 mg, 1.07 mmol) at 0 °C, and the resulting mixture was stirred at 50 °C for 2 d and filtered through a celite pad to give an oil, which was purified by column chromatography to afford an enone (155 mg, 66%) as a yellow oil: ^{1}H NMR δ 1.98−2.20 (m, 2H), 2.61 (dd, 1H, J = 17.6, 2.8 Hz), 2.96 (dd, 1H, J = 17.6, 2.2 Hz), 3.26−3.48 (m, 1H), 3.67 (s, 3H), 3.82 (s, 3H), 4.10−4.53 (m, 2H), 4.66−4.71 (br, 1H), 4.75−5.02 (m, 1H), 6.03 (d, 1H, J = 10.4 Hz), 6.69−6.75 (m, 2H); ^{13}CNMR δ 193.9, 155.8, 147.4, 144.1, 143.4, 129.0, 127.2, 121.4, 120.8, 111.5, 87.6, 56.2, 52.7, 51.9, 51.6, 49.2, 46.0, 37.2; R_f = 0.5 (EtOAc).

To a solution of the enone (46 mg, 0.14 mmol) in THF (3 mL) was added L-Selectride (1 M in THF, 0.16 mL, 0.16 mmol) at −78 °C, and the resulting mixture was stirred at −78 °C to room temperature for 5 h and concentrated to give a solid, which was purified by column chromatography to obtain a colorless solid (46 mg, 99%). To a solution of the solid (24 mg, 0.07 mmol) in THF (1 mL) was added $LiAlH_4$ (10 mg, 0.26 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 d and filtered through

a celite pad to give a colorless solid, which on column chromatography afforded (±)-**9** as a colorless solid (10 mg, 48%). ^{1}H NMR δ 1.60 (dd, 1H, J = 13.8, 1.7 Hz), 2.01 (ddd, 1H, J = 15.7, 5.0, 2.5 Hz), 2.11 (dd, 1H, J = 13.8, 3.3 Hz), 2.21−2.39 (br, 1H), 2.42 (s, 3H), 2.69 (ddd, 1H, J = 15.7, 3.3, 1.7 Hz), 3.08 (brd, 1H, J = 14.0 Hz), 3.28 (d, J = 14.0 Hz, 1H), 3.72 (d, J = 15.4 Hz, 1H), 3.83 (s, 3H), 4.12 (brd, 1H, J = 15.4 Hz), 4.12−4.18 (m, 1H), 4.60−4.62 (br, 1H), 6.00 (d, 1H, J = 10.4 Hz), 6.01 (dd, J = 10.4, 1.2 Hz), 6.63 (d, 1H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz); ^{13}C NMR δ 145.9, 144.3 133.0, 127.8, 126.9, 126.7, 122.2, 111.4, 88.7, 62.1, 60.5, 56.0, 53.8, 48.2, 41.9, 33.7, 30.0 (NMR data are consistent with those reported in the literature[5b]); IR (film) 2978, 1610, 1271 cm^{-1}; R_f = 0.2 (EtOAc); HRMS (EI), m/z 287.1526 (calcd for $C_{17}H_{21}NO_3$ m/z 287.1521).

Total Synthesis of (±)-Mesembrine [(±)-11]. See Supporting Information.

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Supporting Information Available: Representative experimental procedures, physical properties and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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