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Effect of Substitution on the Intramolecular 1,3-Dipolar Cycloaddition of Alkene Tethered Münchnones

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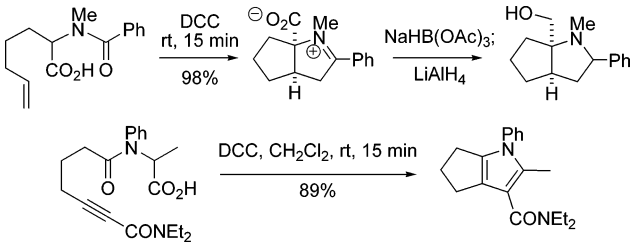

A sequence of chemoselective activation of *N*-acylaminoacids, münchnone generation, intramolecular 1,3-dipolar cycloaddition, and ring opening efficiently generated functionalized polycyclic structures such as cyclopenta[*b*]pyrroles or zwitterionic bicyclo[4.3.0]nonane or bicyclo[3.3.0]octanes in one operation is given. These zwitterionic species were isolated for the first time and were subsequently reduced to bicyclic aminoalcohols. The effect of the substitution of both the dipolarophile and the münchnone on the intramolecular cycloaddition outcome was examined. It was found that either nonactivated or electron-poor alkenes can react with the münchnone if these alkenes are tethered at position 4 on the münchnone (**2**, R^2 = alkene tether), whereas only an electron-poor alkene at position 2 (**2**, R^3 = alkene tether) could undergo successful cycloaddition. Also, münchnones substituted at position 2 with a phenyl (**2**, R^3 = Ph) showed a dramatic increase in reactivity, whereas a phenyl at position 4 (**2**, R^2 = Ph) had a very limited effect.

Introduction

Polysubstituted pyrrole or pyrrolidine containing natural products are extremely abundant in nature. In addition to the rich families of pyrrolizidine and indolizidine alkaloids, one could think of aspidospermanes, strychnanes, mesembranes, tropanes, kopsanes, and erythranes, among others. Most of these alkaloids contain additional rings fused to the pyrrole or pyrrolidine core, conferring a higher degree of molecular complexity. New methods to rapidly access such cores are thus very interesting as a synthetic entry to a wide range of alkaloids. We report herein that the use of münchnones (1,3-oxazolium-5-olates) trapped intramolecularly with a pendent dipolarophile serve this purpose very well: in a single operation, acyclic substrates can be transformed into 1,4,5,6-tetrahydrocyclopenta-[*b*]pyrroles, octahydrocyclopenta[*b*]pyrroles, and octahydroindoles in high yields.

Münchnones **2**, usually prepared from the amido acid precursors **1**,[1] have three sites a dipolarophile tether could be attached to, indicated as R^1, R^2, and R^3 in structure **1** (Scheme 1). Alkene branches at these positions could lead to different cycloadducts following paths A, B, or C. Padwa and co-workers reported examples that showed the viability of path A.[2] However, for the examples of substrates that fell in path C, limited success was achieved.[3] Finally, no intramolecular münchnone−alkene cycloaddition following path B has been reported so far. Paths B and C are extremely interesting and differ substantially from path A in that the cycloadducts **5** and

(1) For a leading reference on the preparation and use of münchnones, see: (a) Gribble, G. W. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa. A., Pearson, W. H., Eds; John Wiley & Sons: Hoboken, NJ, 2003; pp 681−755. For münchnones generated by palladium−catalyzed coupling of imines, acyl chlorides, and carbon monoxide, see: (b) Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474.

(2) (a) Padwa, A.; Gingrich, H. L.; Lim, R. *J. Org. Chem.* **1982**, *47*, 2447. (b) Padwa, A.; Lim, R.; MacDonald, J. G.; Gingrich, H. L.; Kellar, S. M. *J. Org. Chem.* **1985**, *50*, 3816.

(3) Padwa reported three examples of Path C that all gave less than 17% yield of desired cycloadducts (see ref 2a). Their best result is given in Scheme 15, for the formation of pyrrole **56** from münchnone **55**.

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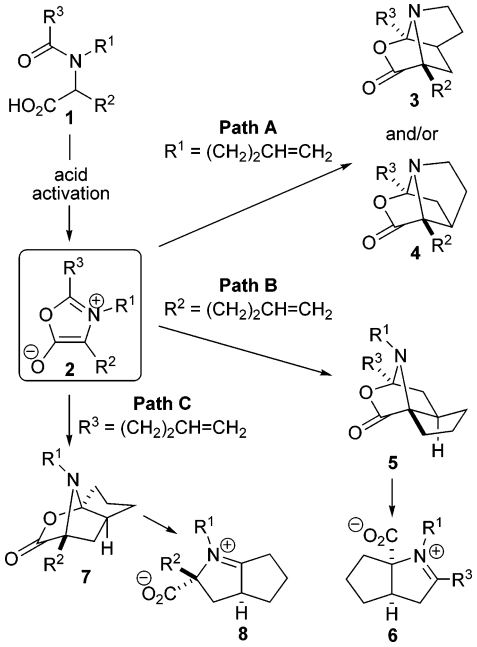
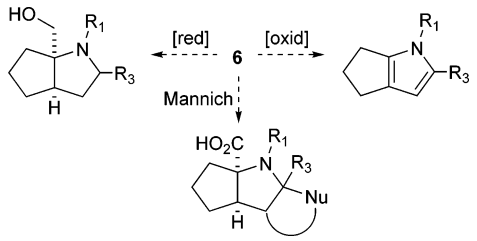
SCHEME 1. Cycloadducts from Differently Substituted Münchnones



SCHEME 2. Possible Transformations of 6



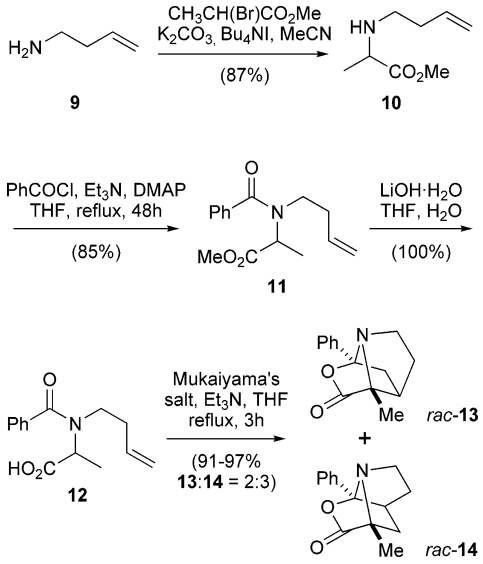
7, compared to **3** and **4**, now have a bridged nitrogen with a lone pair of electrons correctly aligned to allow for the opening of the hemiaminal function. As a result, the zwitterionic species **6** and **8** could be used as functionalized intermediates in the construction of complex alkaloids. They could be further oxidized to the corresponding substituted pyrroles (as shown with **6**, Scheme 2, right), reduced to the aminoalcohols, or eventually trapped in a Mannich cyclization with a tethered π-nucleophile. These transformations lead to valuable building blocks for alkaloid syntheses.

Results and Discussion

We investigated the three different paths of intramolecular 1,3-dipolar cycloaddition of münchnones, as depicted in Scheme 1. So far, the only reported examples following path A all involved substrates bearing an aromatic ring between the dipolarophile and the münchnone.[2] We wanted to verify if fully saturated tethers between the mesoionic ring and the alkene could be used. Because the majority of the natural products that would be accessible through our strategy do not contain an aromatic ring, the use of saturated tethers would thus widen the synthetic applications.

Intramolecular 3 + 2 Cycloaddition Following Path A. A simple model **12** was elaborated from but-3-en-1-amine (**9**): *N*-alkylation followed by benzoylation afforded the amido ester

SCHEME 3. Path A: Synthesis of Substrate 12 and Key Step



11 in good yields (Scheme 3).[4] The ester **11** was then saponified and activated with Mukaiyama's salt (2-chloro-1-methylpyridinium iodide) to give, after only 3 h in refluxing THF, an almost quantitative yield of the expected cycloadducts **13** and **14** (structure of **14** confirmed by single-crystal X-ray diffraction).[5,6]

Intramolecular 1,3-Dipolar Cycloaddition Following Path B. With the assurance that a fully saturated tether between the mesoionic ring and the dipolarophile could efficiently lead to the cycloadduct in yields that were at least as good as those obtained with unsaturated tethers,[2] we started the investigation of path B. The synthesis of the model compounds **20a**−**d** debuted with a Boc protection of sarcosine ethyl ester hydrochloride (**15**, Scheme 4) followed by an alkylation with either 5-iodopent-1-ene or 6-iodohex-1-ene or the iodide **17**[7] derived from the known silyl ether **21a**[8] (Scheme 5). The resulting carbamates **18a**−**c** were cleaved and acylated with either acetyl chloride or benzoyl chloride to give **20a**−**d** after saponification of the ethyl ester.

An *N*-phenyl-substituted substrate was also prepared. Synthesis of **26** started with an *N*-alkylation of *N*-phenylbenzamide (**23**) in 87% yield based on recovered starting material (Scheme 6). *C*-Alkylation of the resulting ester **24** and saponification gave the desired compound **26**.

When the carboxylic acids of **20a**−**c** were activated with DCC[9] at room temperature, a sequence of three transformations

(4) When the alkylation was performed with the benzamide obtained from benzoylation of **9**, the anion of that benzamide was quenched with product **11** as the latter was formed in the reaction mixture.

(5) An ORTEP representation of **14** can be found in the Supporting Information. Crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 628189). The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. or on http://www.ccdc.cam.ac.uk/deposit.

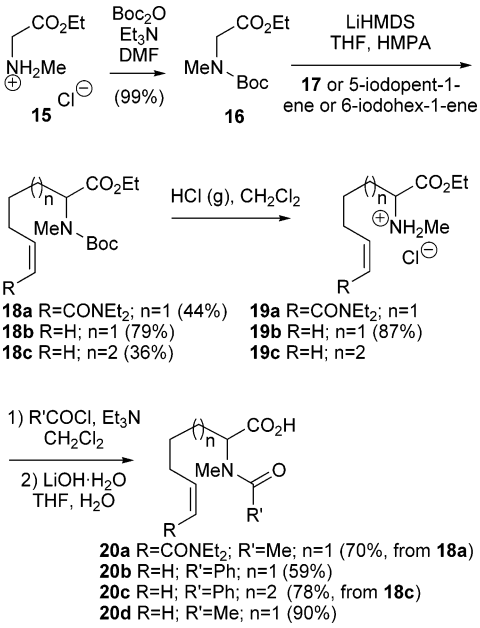
(6) Cycloadducts **13** and **14** were stable and could eventually be reduced, resulting in the opening of the bicyclic core as shown by Padwa with similar compounds (see ref 2b).

(7) *cis*-Iodide **17** was isomerically pure. About 5% of the *trans* isomer was obtained from the previous hydrogenation of alkyne **22a** and was separated at the iodide stage.

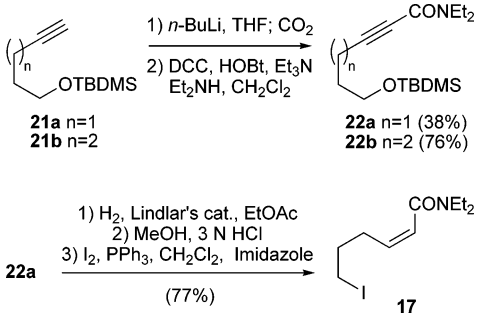
(8) García-Fandiño, R.; Aldegunde, M. J.; Codesido, E. M.; Castedo, L.; Granja, J. R. *J. Org. Chem.* **2005**, *70*, 8281.

(9) Potts, K. T.; Yao, S. *J. Org. Chem.* **1979**, *44*, 977.

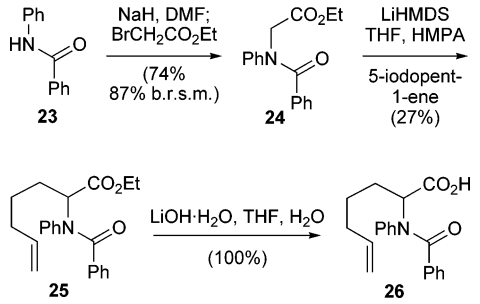
SCHEME 4. Path B: Synthesis of *N*-Methyl Substrates 20a−d



SCHEME 5. Synthesis of Silyl Ether 22b and Iodide 17

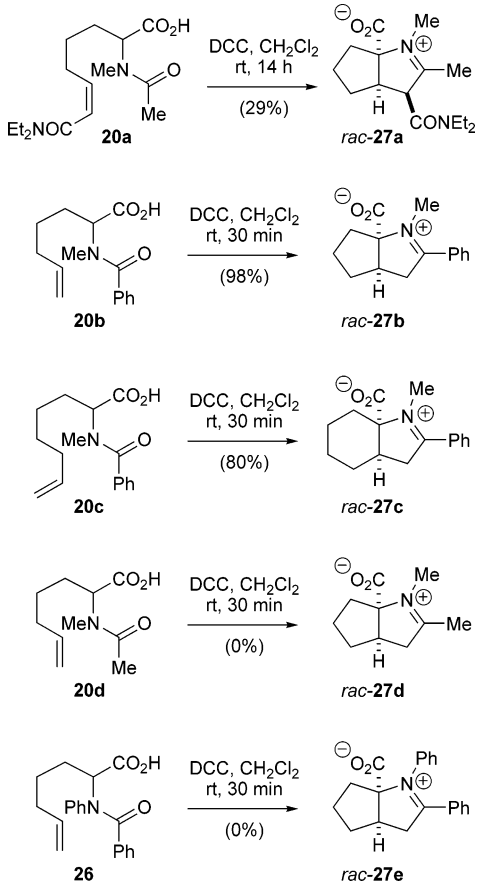


SCHEME 6. Path B: Synthesis of *N*-Phenyl Substrate 26



occurred in 29−98% yield: (1) the corresponding münchnones were generated, (2) these münchnones underwent an intramolecular 1,3-dipolar cycloaddition, and (3) the resulting hemiaminal ring opened to the zwitterionic adducts **27a**−**c** (Scheme 7, following the general sequence **1** → **2** → **5** → **6** of Scheme 1). Besides being the first examples of intramolecular cycloaddition of münchnones following path B (see Scheme 1), the most remarkable aspect of these results is that no decarboxylation of the zwitterionic cycloadducts **27a**−**c** occurred with these reaction conditions.[10] In fact, we were able to isolate the pure zwitterionic products from the aqueous phase, after washing with organic solvents. Unfortunately, treatment of acetamidoacids **20d** and **20e** in the same reaction conditions afforded no cycloadduct.[11] This result will be discussed in a later section (vide infra, Scheme 13).

SCHEME 7. Path B: Tandem Münchnone−Alkene Intramolecular 1,3-Dipolar Cycloaddition and Ring Opening



The zwitterionic products **27a**−**c** could be advantageously used: because of the presence of both an iminium ion and a carboxylate, one could think of reducing both of these functional groups to the corresponding aminoalcohol or trapping the iminium ion in a Mannich addition. The reduction was effectively performed and the aminoalcohols **28b**,**c** were isolated upon a one-pot treatment with $NaHB(OAc)_3$ to reduce the iminium ion then with $LiAlH_4$ to effect the reduction of the carboxylate of **27b**,**c** (Scheme 8).[12] The structure of **28c** (β-Ph) was confirmed by single-crystal X-ray diffraction.[13]

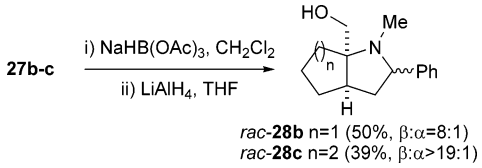
(10) To the best of our knowledge, the closest reported example is the formation of a *neutral* imino acid (not zwitterionic *N*-alkyliminium carboxylate as in our case) that did not decarboxylate and that was obtained in modest yield. See: Maryanoff, C. A.; Karash, C. B.; Turchi, I. J.; Corey, E. R.; Maryanoff, B. E. *J. Org. Chem.* **1989**, *54*, 3790.

(11) In the case of the activation of **26**, the generation of the münchnone intermediate was proven by addition of DMAD, so that the corresponding pyrrole **49c** was isolated in 99% yield. For trapping of münchnones with DMAD, see Scheme 13.

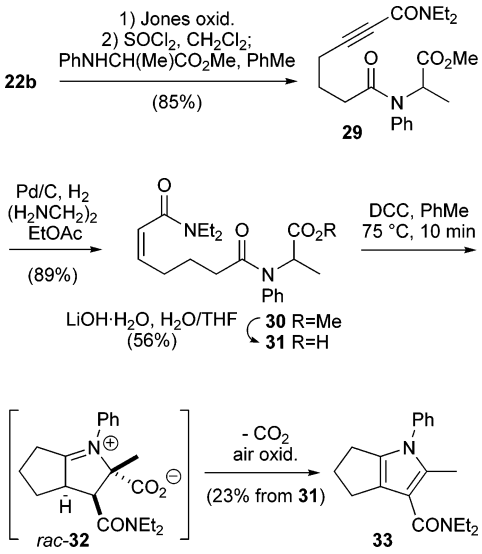
(12) When **27b** was treated with an excess of $LiAlH_4$ alone, a 2:1 mixture of diastereomers was obtained, presumably due to a less stereoselective initial reduction of the iminium ion with $LiAlH_4$ than with $NaHB(OAc)_3$. The major diastereomers of **28b**,**c** were assumed to come from a reduction of the iminium from the convex face of **27b**,**c**.

(13) An ORTEP representation of **28c** can be found in the Supporting Information. Crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre (CCDC No. 628188). The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K. or on http://www.ccdc.cam.ac.uk/deposit.

SCHEME 8. Reduction of the Zwitterionic Adducts 27b,c



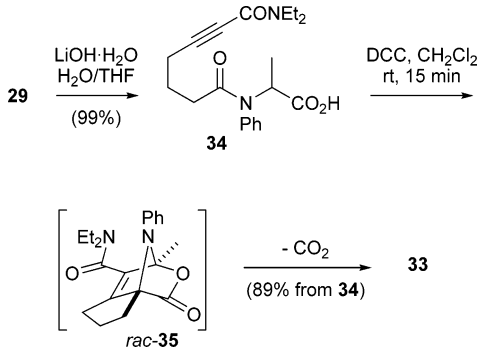
SCHEME 9. Path C: Synthesis of Alkenyl Substrate 31 and Key Step



Intramolecular 1,3-Dipolar Cycloaddition Following Path C. With these results in hand, we turned to the study of path C (cf. Scheme 1). We opted to test the münchnone generation−intramolecular 1,3-dipolar cycloaddition−ring opening cascade with substrates **31** and **34**, both prepared from silyl ether **22b**[14] (Schemes 9 and 10). The latter was hydrolyzed and oxidized with use of Jones' conditions. The resulting carboxylic acid was coupled with methyl 2-(phenylamino)propionate[15] via the acyl chloride intermediate in 85% yield for the two steps. Compound **29** was partially hydrogenated with ethylenediamine to poison the catalyst then quantitatively saponified to the alkene−acid **31**. When the latter was activated with DCC, the formation of the münchnone occurred, followed by intramolecular 1,3-dipolar cycloaddition with the tethered alkene and hemiaminal cleavage. The resulting zwitterionic species **32** spontaneously decarboxylated and was further oxidized with air to the corresponding pyrrole **33**, as the only observed product.[16]

The structure of the pentasubstituted pyrrole **33** was confirmed by the preparation of the same compound through the route depicted in Scheme 10. Although the yield for the formation of pyrrole **33** derived previously from the vinylic amide **31** was somewhat low, a much better conversion was obtained when acetylenic amide **34** was used as the dipolarophile. The desired cascade generated the pyrrole **33** in 89% yield through the cycloadduct intermediate **35** after CO_2 extrusion.[17]

SCHEME 10. Path C: Synthesis of Alkynyl Substrate 34 and Key Step



The electron-poor tethered dipolarophiles of compounds **31** and **34** fruitfully demonstrated the possibility of effecting the key transformation following path C. However, from these results, we did not know if an electron-poor dipolarophile was absolutely needed for the intramolecular cycloaddition following path C. To address this question, a series of substrates were prepared.[18] The elaboration of the model compounds **40a**−**d** started with the amide coupling of acid **38** (or its acyl chloride derivative) with amine **37**, aniline, or 4-methoxyaniline (Scheme 11). The resulting amide **39** was saponified to the amido acid **40a**, whereas amides **41a**,**b** were *N*-alkylated with either methyl 2-bromopropionate or methyl α-bromophenylacetate then saponified to the acids **40b**−**d**.

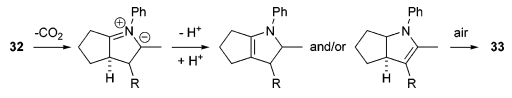
In another sequence, the vinylic chloride **40e** and methyl enol ether **40f** were prepared by Wittig olefinations of a common aldehyde **44** (Scheme 12). The latter was straightforwardly derived from penta-1,5-diol (**42**).

When subjected to the acid activation conditions, **40a**−**f** gave no desired intramolecular cycloadducts **46a**−**f** or any ring-opened products **47a**−**f** or further decarboxylated compounds **48a**−**f** (Scheme 13). This contrasts with the fast and high yielding intramolecular reactions of münchnones bearing non-activated alkenyl dipolarophiles following path B (Scheme 7). For path C, nonactivated alkenes (**45a**−**d)** or slightly electron-poor chloroalkene (**45e**) tethered to the münchnone at the R^3 position were not reactive enough. The electron-rich dipolarophile of **45f** did not give intramolecular cycloaddition either, which might have been envisaged through a reverse electron demand 1,3-dipolar cycloaddition. Nonetheless, it should be noted that in every case the generation of the münchnone intermediate (**45a**−**f**) unequivocally occurred within 30 min at

(14) Guay, B.; Deslongchamps. P. *J. Org. Chem.* **2003**, *68*, 6140.

(15) Prepared by using the procedure described in: Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465. For characterization data, see: Gately, D. A.; Norton, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 3479.

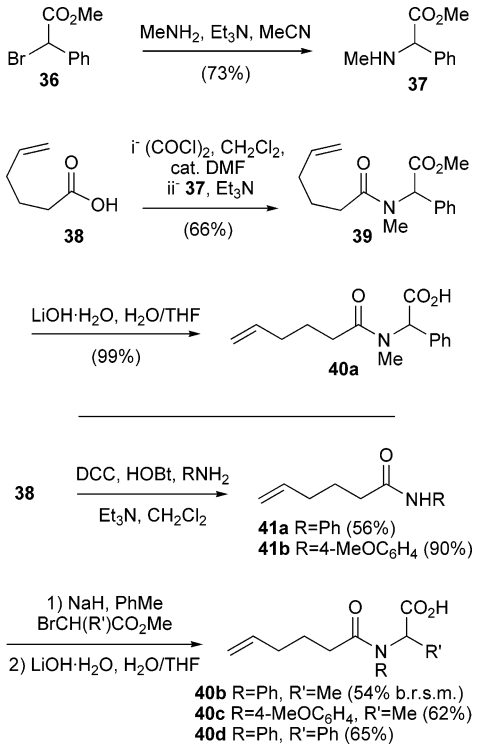
(16) The following proposed mechanism for the decarboxylation and oxidation of the zwitterionic adduct **32** was also suggested by Padwa (see ref 2a):



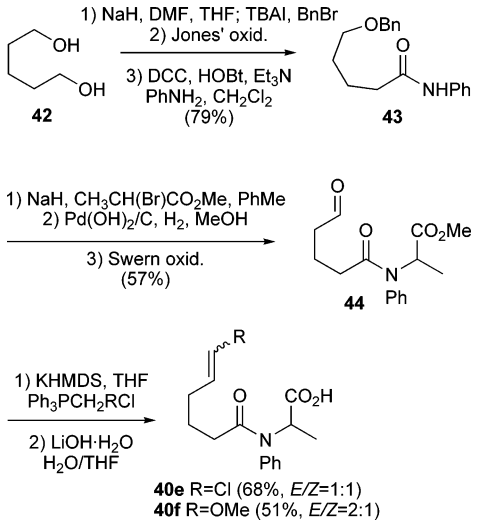
(17) Similar intramolecular *alkyne*−münchnone cycloadditions following path C were reported firstly by Kato with a *meta*-substituted aryle as an unsaturated tether (Kato, H.; Wang, S.-Z.; Nakano, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 361) and later by Padwa (see ref 2b). Tethers containing a ketone also proved to be successful in generating the cycloadducts (Pinho e Melo, T. M. V. D.; Barbosa, D. M.; Ramos, P. J. R. S.; d'A Rocha Gonsalves, A. M.; Gilchrist, T. L.; Beja, A. M.; Paixão, J. A.; Silva, M. R.; Alte da Viega, L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1219). The use of fully saturated tethers between the alkyne and the münchnone was reported by Sainsbury, although modest yields were obtained (Sainsbury, M.; Strange, R. H.; Woodward, P. R.; Barsanti, P. A. *Tetrahedron* **1993**, *49*, 2065).

(18) The preparation of other electron-poor alkenyl dipolarophiles substituted with alkoxycarbonyl, cyano, or nitro groups failed. These substituents did not tolerate the saponification conditions needed to generate the required carboxylic group for the key transformation. The generation of the carboxylic acid prior to the installation of the alkoxycarbonyl, cyano- or nitro-substituted alkene was also unsuccessful.

SCHEME 11. Path C: Synthesis of Substrates 40a−d



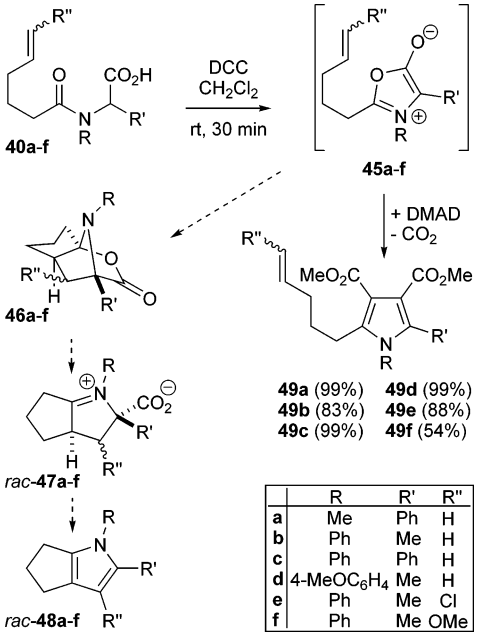
SCHEME 12. Path C: Synthesis of Substrates 40e,f



room temperature upon activation of **40a−f** with DCC,[19] as confirmed by the isolation of the corresponding pyrroles **49a−f** in good to quantitative yield when dimethyl acetylenedicarboxylate (DMAD) was added to the reaction mixture.[20]

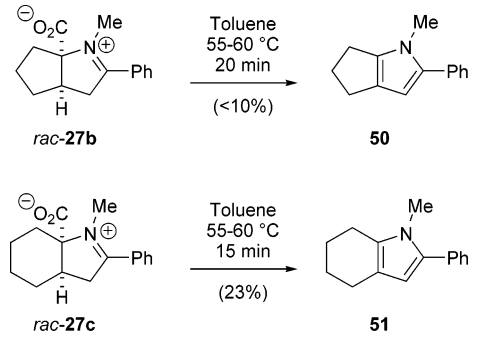
So far, all of our results showed an important difference between the reactivity of alkene tethered münchnones branched at the R^2 position (path B) and those branched at the R^3 position (path C). The former gave the zwitterionic cycloadducts (**27a−c**) with electron-poor dipolarophiles and with unactivated dipolarophiles (Scheme 7), whereas R^3-branched münchnone

SCHEME 13. Path C: Attempted Intramolecular 1,3-Dipolar Cycloadditions



	R	R'	R"
a	Me	Ph	H
b	Ph	Me	H
c	Ph	Ph	H
d	4-MeOC$_6$H$_4$	Me	H
e	Ph	Me	Cl
f	Ph	Me	OMe

SCHEME 14. Decarboxylation of 27b and 27c



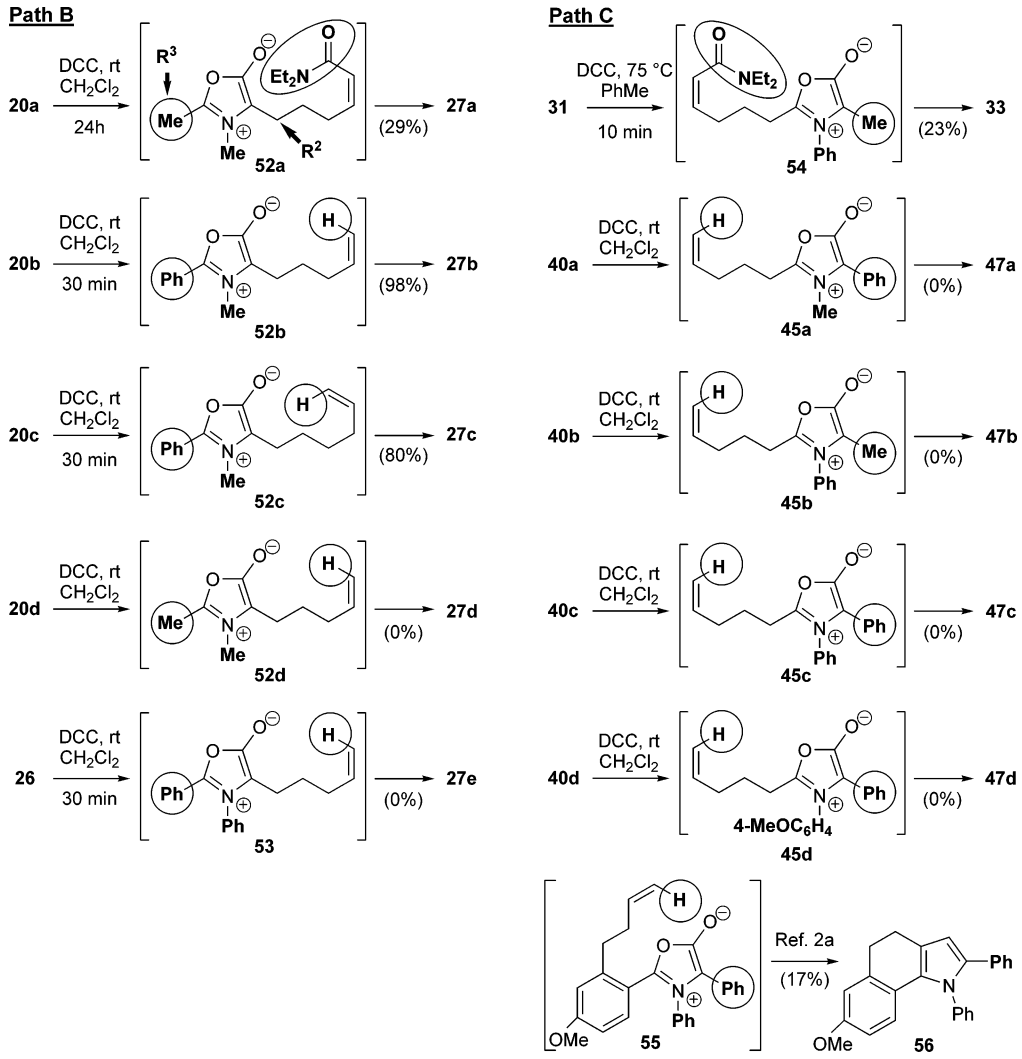
only reacted with an electron-poor dipolarophile (unsaturated ester) and led to the corresponding pyrrole (**33**) after spontaneous decarboxylation of the zwitterionic product (Scheme 9). The difference in the reaction products (zwitterionic adduct versus pyrrole) could be explained by looking at the temperature required for the 1,3-dipolar cycloadditions: For path B, the intramolecular cycloaddition occurred at room temperature (Scheme 7). For path C, the münchnone intermediates were also formed at room temperature (see Scheme 13, where münchnones **45a−f** were trapped intermolecularly with DMAD at room temperature) but the intramolecular 1,3-dipolar cycloaddition required heat (75 °C). Seemingly, the resulting zwitterionic adduct **32** was heat-sensitive and readily decarboxylated to lead to the observed pyrrole **33** (Scheme 9). To verify this hypothesized heat-sensitivity of the zwitterionic adducts, **27b** and **27c** (obtained from path B) were heated to 55−60 °C and were completely consumed within 20 min (Scheme 14). We were able to isolate the corresponding pyrrole **51** from decarboxylation and air oxidation of the zwitterionic compound **27c**,[16] whereas only traces of **50** were identifiable when **27b** was subjected to the same conditions.

These results also suggest that the low yield (23%) obtained for the conversion of substrate **31** to pyrrole **33** (Scheme 9) could be due to the decarboxylation step only, as suggested by

(19) Comparable results were obtained when the activation of the carboxylic acid and generation of the münchnone were initiated with either DCC or Mukaiyama's salt.

(20) The generation of tetrasubstituted pyrroles by intermolecular cycloaddition of münchnones with alkynyl dipolarophiles has already been extensively documented. See ref 1.

SCHEME 15. Effect of Substitution on Intramolecular 1,3-Dipolar Cycloaddition of Alkene-Tethered Münchnones



the yield (23%) obtained for the decarboxylation of **27c** to **51** (Scheme 14). But even though the cycloaddition step in the formation of **33** might be high yielding, this cycloaddition following path C is nonetheless more difficult than any cycloaddition according to path B, as a higher temperature and an electron-poor dipolarophile were absolutely necessary to the success of path C. This brings another interesting question: why are intramolecular 1,3-dipolar cycloadditions of alkene tethered münchnones more difficult following path C than path B? To answer this question, two distinct factors were analyzed: (1) substitution of the dipolarophile and (2) substitution of the münchnone.

Effect of the Substitution of the Dipolarophile on the Intramolecular Münchnone−Alkene 1,3-Dipolar Cycloaddition. It is known that münchnones act as type-I dipoles ($HOMO_{dipole}-LUMO_{dipolarophile}$ control) and prefer to react with electron-poor dipolarophiles,[21] as supported by the Frontier Molecular Orbital (FMO) theory.[22] Indeed, the electron-poor alkenes of **52a** and **54** gave the desired cycloadducts whereas no cycloaddition was observed for their nonactivated alkene parents **52d** and **45b** (Scheme 15).

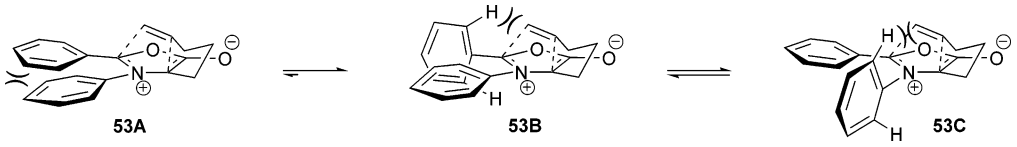
Effect of the Substitution of the Münchnone on the Intramolecular Münchnone−Alkene 1,3-Dipolar Cycloaddition. Switching from a methyl to a phenyl conferred a dramatically different reactivity to the münchnone when that change was made at position R^3 as confirmed by the cycloadditions of **52d** (Me) and **52b** (Ph), giving 0% and 98% yield, respectively (Scheme 15). Interestingly, the difference was apparently not as spectacular when the same switch was made at the R^2 position since both **45b** (Me) and **45c** (Ph) resulted in no cycloaddition. The beneficial effect of a phenyl at the R^3 position was also exemplified in Padwa's group by the cycloaddition of münchnone **55**, bearing an *o*-butenylaryl group at the R^3 position.[2a] This aryl substitution allowed for the intramolecular cycloaddition with a nonactivated alkene (cf. **45c** and **55**).

Additionally and most strikingly, changing the methyl to a phenyl at position R^3 on the münchnone (cf. **52d** and **52b**) was

(21) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, 2717. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838. (c) Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569. (d) Huisgen, R. *J. Org. Chem.* **1976**, *41*, 403.

(22) (a) Dewar, M. J. S. In *Molecular Orbital Theory of Organic Chemistry*; McGraw-Hill: New York, 1969. (b) Dewar, M. J. S.; Dougherty, R. C. In *The PMO Theory of Organic Chemistry*; Plenum Press: New York, 1975. (c) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.

SCHEME 16. Conformational Analysis of Münchnone 53



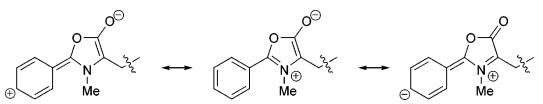
remarkably more beneficial for the cycloaddition than just adding an electron-withdrawing group on the dipolarophile (cf. **52d** and **52a**). The conjugation of a phenyl group with the münchnone (i.e., on the amide carbonyl of the starting material) might in fact play two roles: (1) it increases the reactivity of the münchnone[23] and (2) it increases the thermal stability of the münchnone. These two roles must be amplified when the phenyl is at the R^3 position on the münchnone compared to the R^2 position in order to fit the observations discussed above. The geometry of the reactive conformation should not play an important role in this difference in reactivity because the geometrical constraint imposed to the tether in the reactive conformation is the same for the R^2- and R^3-tethered alkenes. However, when examining electronic factors, a tentative explanation comes up: a phenyl at position R^3 can delocalize both charges of the münchnone through linear conjugation,[24] thus increasing the overall reactivity of the münchnone,[23] whereas a phenyl at position R^2 can only delocalize the negative charge of the münchnone through cross conjugation,[25] which should lower the energy of the münchnone HOMO and render the münchnone less reactive.[23]

Finally, comparison between the high yield of cycloadduct **27b** through münchnone intermediate **52b** and the absence of intramolecular cycloaddition for münchnone **53** tends to indicate a dramatic decrease in reactivity due to the addition of a phenyl substituent on the münchnone nitrogen. By looking at the conformations of münchnone **53**, we find that the latter could simply not adopt a conformation in which both phenyls would be coplanar as in **53A**, due to severe steric interactions between the phenyls (Scheme 16). Instead, one of the phenyls has to be perpendicular to the münchnone plane, as in **53B** or **53C**, thus seriously hindering the approach of the alkenyl dipolarophile.[26]

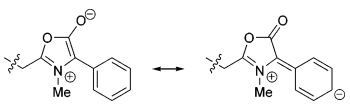
This analysis suggests that the additional phenyl on the nitrogen does not deactivate the münchnone by a conjugation effect (or FMO argument) but rather by a conformational effect. Furthermore, results of path C even tend to reveal that substitution on the münchnone nitrogen has in fact a limited effect on the cycloaddition, since no cycloaddition was observed when going from an *N*-methyl (**45a**), to an *N*-phenyl (**45c**), to an *N*-(4-methoxy)phenyl (**45d**) (Scheme 15). Apparently, the increase in energy of the münchnone HOMO from **45a** to **45c** to **45d** was not sufficient to allow for an intramolecular 1,3-dipolar cycloaddition following path C, whereas the decrease in energy of the dipolarophile LUMO played a beneficial role on the cycloaddition outcome (cf. **45b** and **54**).

(23) Conjugation of a phenyl with a dipole (or a dienophile) reduces the energy of its LUMO and increases the energy of its HOMO, thus giving rise to a more reactive dipole toward both electron-rich and electron-poor dipolarophile (see ref 22c).

(24) Linear conjugation of the phenyl in R^3 with the münchnone:



(25) Cross conjugation of the phenyl in R^2 with the münchnone:



Conclusions

In summary, we successfully developed two reaction sequences leading to either iminium-carboxylate ylides that could be further reduced to bicyclic amino alcohols or pyrrole-containing bicyclic systems. These motifs are extremely abundant in alkaloids' skeletons. The routes that were designed are highly convergent and the tandem münchnone generation−intramolecular 1,3-dipolar cycloaddition−ring opening gave good to high yields of valuable bicycloadducts. As expected, electron-poor alkenes are preferred for the intramolecular 1,3-dipolar cycloaddition of alkene tethered münchnone and could make the difference between no reaction and a successful cycloaddition. Also, a dramatic increase of reactivity for münchnones conjugated with an aromatic ring at the R^3 position (path B) was observed. This conjugation proved to be even more beneficial on the cycloaddition outcome than the effect of adding an electron-withdrawing substituent on the tethered dipolarophile for path B, whereas conjugation of an additional phenyl at the R^2 position was not sufficient for a successful cycloaddition following path C.

Experimental Section

***rac*-6-Methyl-3-phenyl-4-oxa-7-azatricyclo[4.3.0.0^{3,7}]nonan-5-one (13) and 3-Methyl-6-phenyl-5-oxa-7-azatricyclo[4.3.0.0^{3,7}]-nonan-4-one (14).** Et_3N (3.9 mL, 28 mmol) and 2-chloro-*N*-methylpyridinium iodide (Mukaiyama's salt, 0.22 g, 0.84 mmol, dried azeotropically by coevaporations with benzene) were added to a solution of **12** (0.208 g, 0.840 mmol) in THF (14 mL). The reaction mixture was heated at reflux for 4 h, and then concentrated under reduced pressure. The crude material was dissolved in EtOAc and a saturated aqueous solution of $NaHCO_3$ was added. The resulting mixture was vigorously stirred for 5 min, and then the layers were separated. The aqueous phase was extracted with EtOAc. The organic layers were combined, washed with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. A first purification by flash chromatography (silica gel, 30% EtOAc in hexanes) afforded a 2:3 mixture of **13** and **14** (0.188 g, 97%). A second purification by flash chromatography (silica gel, 5% acetone in toluene) afforded **13** (white semisolid) and pure **14** (white solid). **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.64−7.60 (m, 2H), 7.44−7.43 (m, 3H), 2.91 (ddd, J = 13.5, 10.5, 2.5 Hz, 1H), 2.54−2.47 (m, 2H), 2.35 (ddd, J = 12.5, 5.5, 2.5 Hz, 1H), 2.07−1.98 (m, 1H), 1.73 (d, J = 13.5 Hz, 1H), 1.58 (ddd, J = 11.5, 8.0, 2.5 Hz, 1H), 1.44 (s, 3H); IR (film) ν (cm^{-1}) 3001−2890, 1784, 1343; MS (EI) *m*/*z* (rel %)

(26) Münchnone **53** intermediate was successfully trapped with DMAD and gave the corresponding pyrrole. This constituted a proof that **53** was indeed formed from the acid **26** activation. The reaction of **53** with DMAD, compared to the absence of reaction with the tethered alkene, could be understood from two standpoints: (1) DMAD is a highly activated electron-poor dipolarophile compared to the nonactivated tethered alkene and (2) an alkyne is generating much less steric congestion when it approaches a hindered dipolarophile than a substituted alkene does.

229 [M^+] (50), 201 (15), 105 (100); HRMS (EI) calcd for $C_{14}H_{15}NO_2$ [M^+] 229.1103, found 229.1100 ± 0.0007. **14**: mp 139−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.65−7.62 (m, 2H), 7.44−7.41 (m, 3H), 3.08 (dd, J = 5.5, 3.5 Hz, 1H), 2.87 (ddd, J = 13.5, 10.5, 3.5 Hz, 1H), 2.66 (ddd, J = 13.5, 9.0, 7.0 Hz, 1H), 2.00 (ddd, J = 12.5, 5.5, 2.5 Hz, 1H), 1.70−1.58 (m, 1H), 1.52 (ddd, J = 12.5, 9.0, 3.5 Hz, 1H), 1.49 (s, 3H), 1.19 (d, J = 13.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.8, 132.3, 129.8, 128.7, 127.9, 106.2, 69.1, 42.3, 41.0, 36.8, 33.0, 12.7; IR (film) ν (cm^{-1}) 2993−2882, 1801, 1454, 1347; MS (EI) *m*/*z* (rel %) 229 [M^+] (50), 201 (15), 105 (100); HRMS (EI) calcd for $C_{14}H_{15}NO_2$ [M^+] 229.1103, found 229.1100 ± 0.0007.

Zwitterion 27b. DCC (0.147 g, 0.713 mmol) was added to a solution of **20b** (0.169 g, 0.646 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 30 min and then concentrated under reduced pressure. After addition of EtOAc and water, the layers were separated. The aqueous layer was washed with EtOAc and concentrated under reduced pressure. The resulting crude material was dissolved in CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to afford **27b** (0.155 g, 98%) as a brown hygroscopic solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66−7.55 (m, 5H), 3.84 (ddd, J = 19.5, 9.5, 2.5 Hz, 1H), 3.61 (s, 3H), 3.19 (q, J = 7.0 Hz, 1H), 3.07 (d, J = 19.5 Hz, 1H), 2.77 (dt, J = 14.5, 7.0 Hz, 1H), 2.23−2.05 (m, 2H), 1.95 (dqi, J = 12.0, 6.0 Hz, 1H), 1.61 (dqi, J = 14.5, 7.0 Hz, 1H), 1.48 (dq, J = 12.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 183.2, 170.2, 134.1, 129.6, 128.6, 127.1, 96.0, 45.4, 43.2, 37.1, 34.6, 34.2, 25.8; IR (film) ν (cm^{-1}) 3479 (br), 2944, 2869, 1631, 1448, 1367.

***rac*-(1-Methyl-2-phenylhexahydrocyclopenta[*b*]pyrrol-6a-yl)-methanol (28b).** $NaHB(OAc)_3$ (0.343 g, 1.62 mmol) was added to a solution of **27b** (0.127 g, 0.521 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The reaction mixture was allowed to warm slowly to room temperature then was stirred at room temperature for 12 h under nitrogen flow to remove CH_2Cl_2. THF (10 mL) and $LiAlH_4$ (0.160 g, 4.22 mmol) were added. The reaction mixture was heated at reflux for 3 h then cooled to room temperature. Distilled water and a 1 N solution of NaOH were added to the reaction mixture. The white suspension was then filtered on a pad of Celite (Et_2O washings). The layers were separated and the organic layer was washed with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (silica gel, 20 to 50% EtOAc in hexanes) to afford **28b** (0.061 g, 50%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) as a 8:1 mixture of diastereomers, 7.39−7.21 (m, 5H), 3.88 (d, J = 11.0 Hz, 1H), 3.83 (dd, J = 10.5, 6.0 Hz, 1H), 3.61 (d, J = 11.0 Hz, 1H), 3.52 (d, J = 10.5 Hz, 1H, minor diastereomer), 3.31 (d, J = 10.5 Hz, 1H, minor diastereomer), 2.52−2.44 (m, 1H), 2.37 (dd, J = 12.0, 5.5 Hz, 1H), 2.34 (dd, J = 12.0, 5.5 Hz, 1H), 2.21 (s, 3H), 2.00 (s, 3H, minor diastereomer), 1.99−1.82 (m, 2H), 1.69−1.50 (m, 4H), 1.31 (ddd, J = 12.0, 10.0, 8.0 Hz, 1H), 1.16 (td, J = 12.0, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) as a 8:1 mixture of diastereoisomers, 144.4, 128.4, 128.2, 127.1, 126.9, 75.7, 69.6, 68.5, 66.9, 64.2, 44.0, 43.7, 42.6, 34.4, 33.9, 32.9, 32.2, 29.2, 26.0, 24.3; IR (film) ν (cm^{-1}) 3406 (br), 2945, 2860, 2787, 1453, 759, 700. MS (EI) *m*/*z* (rel %) 231 [M^+] (1), 200 [$(M - CH_2OH)^+$] (100); HRMS (EI) calcd for $C_{15}H_{21}NO$ [M^+] 231.1623, found 231.1619 ± 0.0007.

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Supporting Information Available: Experimental procedures for compounds **10**−**12**, **16**−**18c**, **19b**, **20a**−**d**, **22a**,**b**, **24**−**27a**, **27c**, **28c**−**31**, **33**, **34**, **37**, **39**−**41b**, **43**, **44**, **49a**−**f**, and **51**, ^{1}H and ^{13}C NMR spectra for compounds **10**−**14**, **16**−**18c**, **19b**, **20a**−**22b**, **24**−**31**, **33**, **34**, **37**, **39**−**41b**, **43**, **44**, **49a**−**f**, and **51**, and crystallographic data for compounds **14** and **28c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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