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A Stereoselective and Atom-Efficient Approach to Multifunctionalized Five- and Six-Membered Rings via a Novel Michael-Initiated Intramolecular Diels–Alder Furan Reaction

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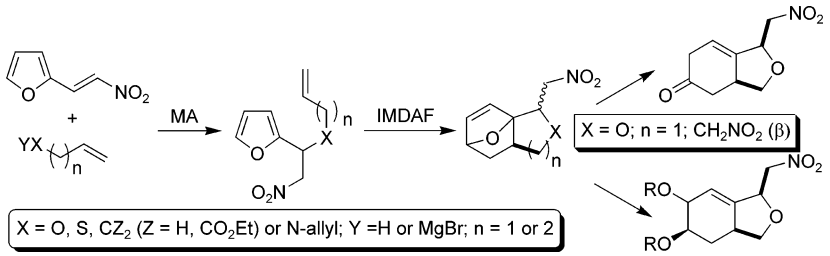

A variety of key precursors to the intramolecular Diels–Alder reaction of furan diene (IMDAF) have been prepared via a very facile 1,4-addition of O-, S-, N-, and C-centered nucleophiles possessing unsaturated tether to β-furyl nitroethylene. Subsequent IMDAF reaction of the 1,4-adducts, carried out under thermal conditions, provided five- and six-membered carbocycles and heterocycles fused to an easily cleavable oxabicycloheptene moiety. The structure and stereochemistry of the cycloadducts were determined by 2D-NMR experiments and further confirmed by X-ray crystallography. The salient features of the strategy include high degree of stereoselectivity (>80:20) in the cycloaddition, atom and step economy, and generation of multiple chiral centers and functionalities. The feasibility of the cleavage of the oxa bridge in the cycloadducts to afford novel multifunctional molecules has also been demonstrated.

Introduction

The dienic reactivity of five-membered heteroaromatic compounds such as furans, thiophenes and pyrroles is well-documented in the literature.[1] The resulting heteroatom-bridged norbornenes or norbornadienes are valuable precursors to functionalized cyclohexenes. Furans, in particular, take part in inter- and intramolecular Diels–Alder reactions with a variety of dienophiles such as alkenes, alkynes (including benzynes) and allenes.[2] The intramolecular Diels–Alder reaction[3–5] of furan diene (IMDAF) is particularly attractive as two or more rings can be constructed in a single step with high regio- and stereocontrol, providing a convenient entry into polycyclic targets including natural products.[1,2,5] However, the paucity of general and convenient methods for the synthesis of IMDAF precursors and the scarcity of

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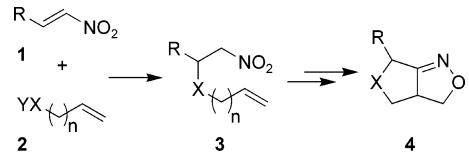
structural diversity in the IMDAF products curtailed the scope and potential of the IMDAF reaction as a strategy of choice for synthetic chemists.

From the perspective of natural product synthesis, stereoselective synthesis of functionalized cyclopentane, cyclohexane and their heteroatom (N, O, S) analogues are of immense interest owing to the ubiquitous presence of these rings in innumerable bioactive natural products.[6] Although these five- and six-membered rings are accessible via independent and often elegant routes, general and viable methodologies that are easily adaptable, for instance, for the quick generation of libraries of potentially active organic compounds would be invaluable in medicinal chemistry and allied areas.

From yet another perspective, conjugated nitroalkenes are distinguished by their versatile reactivity as Michael acceptors, dienophiles, heterodienes, 1,3-dipoles, etc.[7] The nitro group, by virtue of its umpolung of reactivity and ability to undergo facile transformation to a variety of useful intermediates, is a well-recognized functionality in organic synthesis.[8] The ω-nitroalkenes **3** arising from the Michael-type addition of nucleophiles possessing an unsaturated tether **2** to conjugated nitroalkenes **1** are excellent sources of reactive 1,3-dipoles such as nitrile oxides and silyl nitronates, which undergo very facile intramolecular 1,3-dipolar cycloaddition to isoxazolines **4** (Scheme 1).[9,10]

It turns out that if the substituent β to the nitro group in **3** is a reactive functionality such as a furyl group, a whole new sequence of reactions emerges because of the possibility of an intramolecular Diels−Alder reaction between the furyl moiety and the unsaturated tether. Herein, we report on a convenient Michael-initiated IMDAF reaction strategy using conjugated nitroalkenes as the Michael acceptors for the stereoselective synthesis of functionalized five- and six-membered carbocycles and heterocycles. For the first time, to our knowledge, the Michael acceptor ability of conjugated nitroalkenes possessing a reactive substituent β to the nitro group (e.g., β-furyl nitroethylene) has been exploited for the synthesis of IMDAF precursors.

SCHEME 1



Results and Discussion

The IMDAF precursors **6** were synthesized via Michael addition of nucleophiles possessing an unsaturated tether **2** to furyl nitroalkene **5**, which in turn was either commercially available or easily accessible via nitroaldol (Henry) reaction (Table 1). Subsequent transformation of the compounds **6** to the IMDAF cycloadducts **7** and **8** was achieved by heating **6** in appropriate solvents such as toluene, xylene, etc. Thus, the Michael addition of allyl alcohol **2a** in the presence of potassium *tert*-butoxide to furyl nitroalkene **5** at −10 °C in THF provides the β-furyl β-allyloxynitroethane **6a** in 72% yield (Table 1, entry 1). The Michael adduct **6a** underwent IMDAF cycloaddition to the tricyclic systems **7a** and **8a** in a total yield of 67% when a solution of **6a** in toluene was refluxed for 4 days. The remarkable feature of the IMDAF reaction is the diastereoselective formation of **7a** (**7a**:**8a** = 81:19) in which a tetrahydrofuran ring possessing a nitromethyl group is stereoselectively (exo) fused to an oxabicycloheptenyl moiety.

In a similar fashion, the Michael adduct **6b**, prepared in 94% yield via the triethylamine-mediated conjugate addition of allyl mercaptan **2b** to β-furyl nitroalkene **5** (Table 1, entry 2), when heated in xylene under reflux for 4 days provided the tricyclic tetrahydrothiophenes **7b** and **8b** in a total yield of 57% and high stereoselectivity (**7b**:**8b** = 88:12).

Construction of a nitromethyl cyclopentane ring exo-fused to oxanorbornene via the Michael addition of C-centered nucleophiles followed by the IMDAF reaction has also been carried out. The C-nucleophiles included homoallyl Grignard reagent (arising from homoallyl bromide **2c**) and C-allylated diethyl malonate **2d**. Although the 1,4-addition of homoallyl Grignard reagent arising from **2c** to furyl nitroalkene **5** provided the adduct **6c** in very good yield (78%), attempted IMDA reaction between the furyl moiety and the unactivated unsatur-

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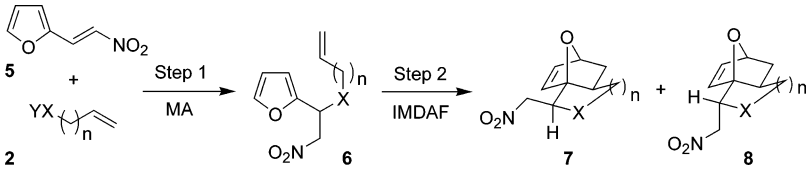
TABLE 1. Michael Addition of C-, N-, O- and S-Centered Nucleophiles 2 to Furyl Nitroalkene 5 and Subsequent IMDAF Reaction of the Michael Adducts 6



entry	**2**, **6**, **7**, **8**	X	Y	n	step 1 (Michael addition) reagents and conditions	% yield of **6**	step 2 (IMDAF) solvent and conditions	% yield of **7** + **8**[a]	**7**:**8**[b]
1	**a**	O	H	1	^{t}BuOK,THF, −10 °C, 15 min	72	toluene, reflux, 4 d	67	81:19
2	**b**	S	H	1	Et_3N, THF, 0 °C−rt, 12 h	94	xylene, reflux, 4 d	57	88:12
3	**c**	CH_2	Br	1	Mg,[c] THF, −78 °C, 15 min	78	xylene, reflux, 4 d	*d*	*d*
4	**d**	CZ_2[e]	H	1	NaH, THF, 0 °C−rt, 45 min	61	toluene, reflux, 2 d	70	85:15
5	**e**	NR[f]	H	1	THF, reflux, 7 d	*g*	THF, reflux, 7 d	45[h]	83:17
6	**f**	O	H	2	^{t}BuOK,THF, −10 °C, 15 min	75	mesitylene, 150 °C, 3 d	59[i]	100:0
7	**g**	CZ_2[e]	H	2	NaH, THF, −20 °C, 30 min	72	xylene, reflux, 3 d	50	100:0
8	**h**	CH_2	Br	2	Mg,[c] THF, −78 °C, 15 min	76	mesitylene, 145 °C, 2.5 d	18[j]	100:0

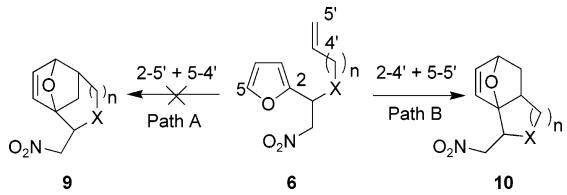
[a] Isolated yield. [b] Ratio of isomers after separation (except in the case of entry 5 where the ratio of the inseparable isomers has been obtained by ^{1}H NMR integration). [c] Grignard formation (THF, rt, 1.5 h). [d] Intractable mixture, similar result was obtained under a variety of other conditions, e.g., (i) mesitylene, 145−165 °C, (ii) xylene or mesitylene, sealed tube, 150−200 °C. [e] Z = CO_2Et. [f] R = allyl. [g] **6e** was not isolated, but allowed to undergo IMDAF reaction in the same pot. [h] 27% of furyl nitroalkene **5** was recovered. [i] 32% **6f** was recovered. [j] 20% **6h** was recovered.

ated tether in **6c** failed even under forcing conditions (Table 1, entry 3). However, much to our delight, the Michael adduct **6d**, prepared in 61% yield by the sodium hydride mediated addition of diethylallyl malonate **2d** to furyl nitroalkene **5**, underwent smooth IMDAF reaction in high yield (70%) and selectivity (**7d**:**8d** = 85:15) when a solution of **6d** was refluxed in toluene for 2 days (Table 1, entry 4).[11]

Having constructed stereoselectively fused and functionalized tetrahydrofuran, tetrahydrothiophene and cyclopentane rings, we turned our attention to the synthesis of pyrrolidine ring via our Michael-IMDAF strategy. Although the Michael addition of amines to nitroalkenes takes place rapidly, it suffers from the competitive retro-Michael addition unless the incipient Michael adduct is transformed to another product.[12] Therefore, we performed the Michael addition of diallylamine **2e** and the subsequent IMDAF reaction of the Michael adduct **3e** in a tandem one-pot sequence, i.e., without isolating the Michael adduct **6e** (Table 1, entry 5). Although the yield is moderate (45% for two steps), good stereoselectivity (**7e**:**8e** = 83:17) is observed in this case as well.

Finally, we set out to carry out the construction of six-membered rings. Michael addition of homoallyl alcohol **2f** to furyl nitroalkene **5** (75% yield) and subsequent IMDAF reaction of the adduct **6f** provided the nitromethyl-substituted tetrahydropyran ring exo-fused to the oxabicycloheptenyl moiety **7f** (59% yield) with remarkable stereoselectivity (**7f**:**8f** = 100:0, Table 1, entry 6). Similarly, a cyclohexane ring fused to the oxabicycloheptenyl moiety was also constructed in a highly stereoselective fashion (**7g**:**8g** = 100:0) via the Michael addition of C-homoallylated diethylmalonate **2g** to β-furyl nitroalkene **5** (72% yield) followed by IMDAF reaction of the

SCHEME 2



Michael adduct **6g** (50% yield, Table 1, entry 7). Although the IMDAF reaction of **6c** possessing an unactivated unsaturated tether failed, the analogous reaction of **6h** was attempted[13] in the hope that the chain extension would relieve the geometric constraints, at least in part, and provide the desired IMDAF product. Indeed, the product was isolated as a single isomer **7h**, albeit in low yield (18%, Table, entry 8).

Although the Michael adducts **6a,b**, **6d** and **6f,g** were purified by column chromatography and fully characterized before being subjected to the IMDAF reaction,[14] it has been observed that the crude Michael adducts could be directly subjected to the IMDAF reaction without any appreciable difference in the overall yields for the two steps, thus further simplifying the procedure to a nearly one-pot reaction (see Supporting Information).

Structure and Stereochemistry. In principle, the Michael adduct **6** could undergo intramolecular cycloaddition via Path A (2−5′ + 5−4′ bonding) or Path B (2−4′ + 5−5′ bonding, Scheme 2). However, the geometric constraints appear to disfavor path A. The favored route, path B, provides IMDAF product **10**, which possesses four chiral centers, out of which two, including one quaternary chiral center, are bridgehead centers and are not variable. Four diastereomers **7**, **8**, **11** and **12** are still possible for the cycloadduct **10** (Scheme 3). However, in our hands, formation of the two diastereomers **7** and **8** in which one of them (**7**) is in overwhelming predominance has been observed. The formation of the exo-fused products **7** and

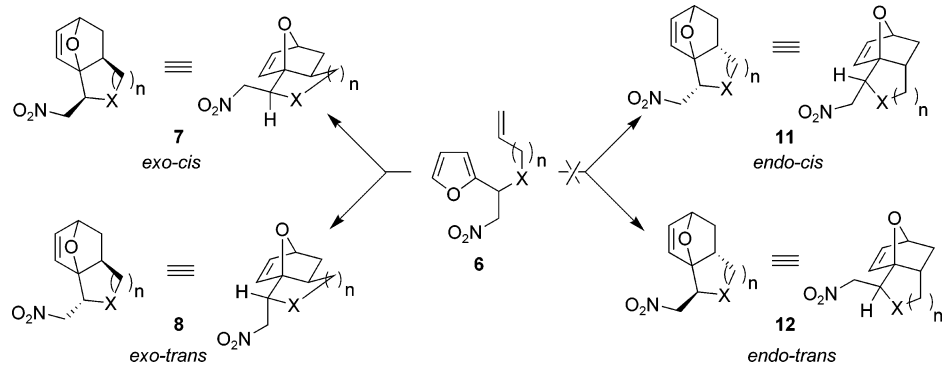
(11) The torsional effect offered by the two ester moieties (*gem*-dicarbalkoxy effect) is presumably playing a major role in facilitating the cycloaddition of **6d**. For studies on the substituent effects on the IMDAF reaction, see: Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 2968.

(12) For instance, trapping of the nitronate arising from the Michael addition of amine to nitroalkene as silylnitronate using TMSCl; see: Gottlieb, L.; Hassner, A. *J. Org. Chem.* **1995**, *60,* 3759.

(13) We thank one of the reviewers for recommending this reaction.

(14) Michael adduct **6c** does not undergo IMDAF reaction and **6e** does in situ.

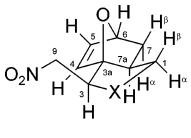
SCHEME 3

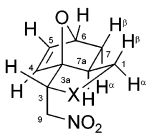


8 under thermodynamic conditions is consistent with the literature.[1,2,5,15,16] Furthermore, the cycloadduct **7** in which the nitromethyl group is β-oriented to minimize nonbonded interactions is favored over the cycloadduct **8** in which the nitromethyl group is α-oriented. Thus, the IMDAF product **10** (Scheme 2) arises from a highly atom economical two-step reaction sequence involving a very facile Michael addition of a variety of nucleophiles (C-, N-, O- and S-centered) possessing an unsaturated tether **2** to furyl nitroalkene **5** and subsequent stereoselective IMDA between the furan diene and the unsaturated tether in the Michael adduct **6**. Such sequential reactions offer a high degree of synthetic efficiency in that they permit complex molecules to be constructed in a simple manner with great elegance and selectivity.[17]

The structure and stereochemistry of all of the cycloadducts were established by analysis of their ^{1}H, ^{13}C, 2D-COSY and 2D-ROESY NMR data (see also Experimental Section). For instance, that the newly formed ring is exo-fused to the oxanorbornene moiety in both **7** and **8** is evident from their relevant ^{1}H−^{1}H couplings (Table 2). This is explained by taking isomers **7b** and **8b** as representative examples for five-membered ring systems **7a**−**e** and **8a**−**e**. Thus, out of the two geminal protons H-7α and H-7β, only H-7β couples with H-6 (J = 4.4 and 4.5 Hz, respectively, in **7b** and **8b**, entries 1 and 2). The absence of any coupling between H-6 and H-7α is attributable to a dihedral angle of ca. 90° between the two protons. On the other hand, whereas H-7α has substantial coupling (J = 7.4 and 7.5 Hz, respectively, in **7b** and **8b**) with H-7a, coupling between H-7β and H-7a is weak (J = 2.5 Hz in both **7b** and **8b**, entries 4 and 5). This is further confirmed by analysis of the 2D-ROESY NMR data for the two isomers. Although there is a weak NOE between H-6 and H-7β, there is no NOE between H-6 and H-7α in both isomers (entries 1 and 2). Similarly, a medium (in **7b**) or strong (in **8b**) NOE is observed between H-7α and H-7a indicating their orientation on the same (endo) side of the oxanorbornene framework (entry 4). Furthermore, either no (in **7b**) or very weak (in **8b**) NOE is observed between H-7β and H-7a (entry 5).

TABLE 2. Comparison of Isomers 7a−e with 8a−e in Terms of *J* Values and NOE Data for Representative Systems 7b and 8b


7a-e


8a-e

		7b		8b	
entry	^{1}H−^{1}H	J in Hz	NOE	J in Hz	NOE
1	6−7α	0.0	−	0.0	−
2	6−7β	4.4	weak	4.5	weak
3	7α−7β	11.7	strong	12.0	strong
4	7α−7a	7.4	medium	7.5	strong
5	7β−7a	2.5	−	2.5	weak
6	7a−1α	7.3	strong	10.5	strong
7	7a−1β	10.7	medium	10.5	medium
8	1α−1β	10.7	strong	11.0	strong
9	3−9	17.1	strong	7.5	strong
10	3−9′	9.6	strong	7.0	strong
11	3−4	−	weak	−	−
12	4−9,9′	−	−	−	weak

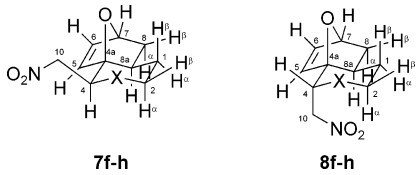
As for the stereochemistry at position 3, considerable difference was discernible in the coupling of H-3 with the nitromethyl protons H-9 and H-9′ in **7b** (J = 17.1 and 9.6 Hz, respectively) but not in **8b** (J = 7.5 and 7.0 Hz, respectively, entries 9 and 10). Although this information appeared insufficient to draw any satisfactory conclusion with regard to the orientation of the nitromethyl group owing to the absence of any other couplings for H-3, a weak NOE between H-3 and H-4 (H-4 and H-5 overlap) in **7b** and between one of the protons of the nitromethyl group, e.g., H-9 and H-4 in **8b**, indeed suggested that the nitromethyl group is β-oriented in **7b** and α-oriented in **8b** (entries 11 and 12). This was further unequivocally established by single-crystal X-ray structure analysis of **8b** (see Supporting Information).[18]

As far as the IMDAF products in which a tetrahydropyranyl and a cyclohexyl moiety are fused to the oxabicycloheptenyl moiety **7f**, **7g**, and **7h**, respectively, are concerned, the assignment of structure and stereochemistry by analysis of their NMR spectral characteristics was much more difficult for two major reasons (Figure 1).[19] First of all, since the cyclization to the six-membered ring was 100% stereoselective, single isomers were

(15) (a) Sader-Bakaouni, L.; Charton, O.; Kunesch, N.; Tillequin, F. *Tetrahedron* **1998**, *54*, 1773. (b) Heiner, T.; Kozhushkov, S. I.; Noltemeyer, M.; Haumann, T.; Boese, R.; de Meijere, A. *Tetrahedron* **1996**, *52*, 12185. (c) Woo, S.; Keay, B. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1411. (d) Ghosh, T.; Hart, H. *J. Org. Chem.* **1989**, *54*, 5073.

(16) Endo-fused (kinetic) products are normally formed under high-pressure-mediated conditions; for a recent example, see: Brickwood, A.; Drew, M. G. B.; Harwood: L. M.; Ishikawa, T.; Marais, P.; Morisson, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 913; see also ref 2.

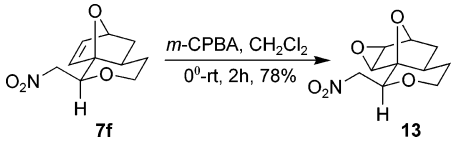
(17) Reviews on sequential reactions: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.



7f-h **8f-h**

FIGURE 1.

SCHEME 4



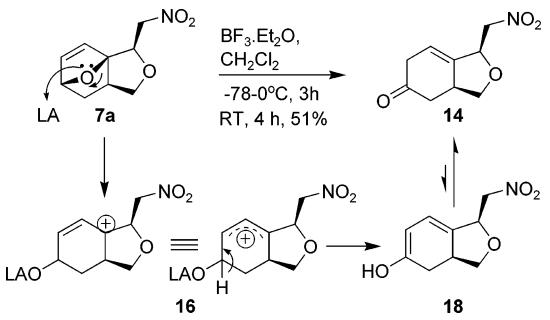
7f **13**

isolated in both the cases and, therefore, no comparison between isomers could be possible. Second, considerable overlapping of the key resonances, i.e., signals corresponding to H-8α, H-8β, H-8a, H-1α and H-1β, was encountered in the IMDAF products **7f**, **7g**, and **7h**.

Finally, single-crystal X-ray structure analysis of **13**, the solid epoxide derivative of **7f**, unambiguously established the structures of six-membered rings fused to the oxabicycloheptenyl moiety **7f**, **7g**, and **7h**.[20] The IMDAF products **7** and **8** are distinguished by the presence of a strategically located nitroalkyl moiety that would be amenable for a legion of transformations such as conversion to 1,3-dipoles, viz., nitrile oxides and silyl nitronates, primary alkyl radicals, oxidation to carboxylic acids, reduction to oximes, hydroxylamines or amines, to name a few.[21−23] Besides the possibility of transforming the nitro group and the nitroalkyl moiety in the IMDAF product **7** or **8** to useful functionalities, the oxabicycloheptenyl moiety in **7** or **8** per se provides a convenient entry into stereoselectively functionalized cyclohexenes fused to five- or six-membered carbocycles or heterocycles. Such ring-opening reactions of oxabicyclic alkenes[21] have been adopted for the facile synthesis of conduritols[22] and pseudo-sugars.[23]

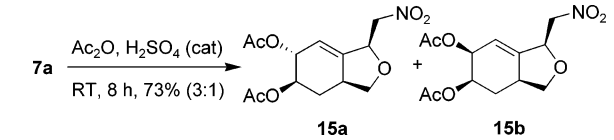
To demonstrate the feasibility of the above-mentioned transformations, the following representative reactions of the oxabicycloheptenyl moiety in the IMDAF products **7** and **8** have been carried out. Thus, treatment of **7a** with $BF_3.Et_2O$ in CH_2Cl_2 afforded the β,γ-enone **14** in 51% yield. A mechanistic rationale for the formation of enone **14** is also outlined in Scheme 5. The mechanism presumably involves the Lewis acid (BF_3•Et_2O) catalyzed ring opening of **7a** to form the allylic cation **16**, which upon proton exchange and decomplexation affords the enol **18**, which tautomerizes to the β,γ-enone **14**.

SCHEME 5



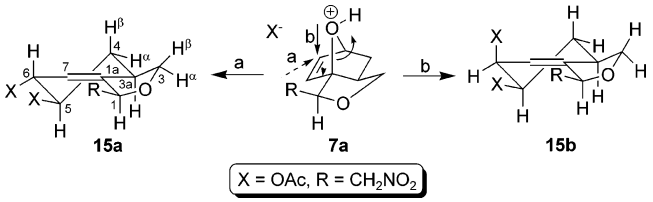
16 **18**

SCHEME 6



15a **15b**

SCHEME 7



15a **7a** **15b**

An alternative method has also been employed for the ring opening of **7a**. For instance, acetolysis of **7a** using acetic anhydride and catalytic amount of sulfuric acid provided a mixture of stereoisomeric diacetates **15a** and **15b** (3:1 ratio) in 73% yield (Scheme 6). The formation of the two stereoisomers has been rationalized in terms of the two modes of ring opening as depicted in Scheme 7.

Analysis of the ^{1}H and ^{13}C NMR data of **15a** and **15b** suggested that the only difference between the two isomers is that they are epimeric at C-6. For instance, ^{13}C NMR (SEFT) showed that in both isomers **15a** and **15b**, one of the olefinic carbon atoms was methine, appearing at 117.1 and 116.1, respectively, and the other quaternary, at 145.1 and 145.8, respectively. Similarly, the ^{1}H NMR spectral analysis with the help of 2D-COSY experiment indicated that H-5 and H-6 are oriented in a pseudo-1,2-diaxial fashion (J = 12.2 Hz) in **15a** and in a pseudo-1,2-axial,equatorial fashion (J = 3.6 Hz) in **15b**. However, the 2D-NOESY data, although supporting the above assignment of most of the individual protons, showed very similar NOE between the key resonances H-5 and H-6 in both the isomers. Therefore, the structures **15a** and **15b** were unambiguously assigned by single-crystal X-ray analysis of the major isomer **15a**.[24]

Summary and Conclusions

The 1,4-adducts arising from addition of a variety of O-, S-, N- and C-centered nucleophiles possessing an unsaturated tether to β-furyl nitroethylene undergo

(18) Selected X-ray crystallographic data for **8b**: $C_9H_{11}NO_3S$, M = 213.25, triclinic P-1, a = 5.6300(3) Å, b = 9.5080(5) Å, c = 9.7400(10) Å, V = 483.63(6) Å^3, Z = 2, D_{calc} = 1.464 g cm^{-3}, μ = 0.314 mm^{-1}, R_1 = 0.0394, R_w = 0.0897.

(19) Trivial numbering for structures **7f**−**h** and **8f**−**h** in Figure 1. For correct nomenclature, see Experimental Section.

(20) Selected X-ray crystallographic data for **13**: $C_{10}H_{13}NO_5$, M = 228.09, triclinic P-1, a = 8.1670(13) Å, b = 10.7620(12) Å, c = 11.823-(2) Å, V = 1007.9(3) Å^3, Z = 2, D_{calc} = 1.497 g cm^{-3}, μ = 0.121 mm^{-1}, R_1 = 0.0558, R_w = 0.1285.

(21) A recent review: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. See also refs 2b and 5a.

(22) (a) Baran, A.; Kazaz, C.; Segen, H.; Sütbeyaz, Y. *Tetrahedron* **2003**, *59*, 3643. (b) Le Drian, C.; Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 338.

(23) (a) Ogawa, S.; Uemura, M.; Fujita, T. *Carbohydr. Res.* **1988**, *177*, 213. (b) Ogawa, S.; Nakamura, K.; Takagaki, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2956.

(24) Selected X-ray crystallographic data for **15a**: $C_{13}H_{17}NO_7$, M = 299.28, monoclinic P 21/n, a = 8.5280(10) Å, b = 10.6700(7) Å, c = 16.3100(10) Å, V = 1445.7(2) Å^3, Z = 4, D_{calc} = 1.375 g cm^{-3}, μ = 0.113 mm^{-1}, R_1 = 0.0450, R_w = 0.1037.

intramolecular Diels−Alder furan reaction upon prolonged heating in a suitable solvent. This two-step Michael-initiated intramolecular Diels−Alder furan reaction strategy, taking advantage of the Michael acceptor ability of a conjugated nitroalkene, enables one to synthesize five- and six-membered rings, both carbocyclic and heterocyclic, with high structural diversity, stereoselectivity and atom economy. Representative examples of facile transformation of the cycloadducts to useful multifunctional molecules via selective cleavage of the oxa-bridge are also presented.

Experimental Section

2-[1-(Allyloxy)-2-nitroethyl]furan (6a). A solution of allyl alcohol **2a** (1.38 g, 24 mmol) in THF (25 mL) was stirred at −10 to −20 °C, while KOBu^t (3.38 g, 30 mmol) was added in small portions. After all of the base had dissolved, a solution of 2-furyl nitroalkene **5** (2.79 g, 20 mmol) in THF (15 mL) was added dropwise over 15 min. After continued stirring for another 15 min, the reaction mixture was cooled to 0 °C and AcOH (2.5 mL) was added, followed by water (20 mL). The reaction mixture was extracted with CH_2Cl_2 (2 × 40 mL) and the combined organic layers were washed with water (25 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:9) as eluent to afford pure **6a**. Light yellow oil: yield 2.84 g, 72%; IR (film, cm^{-1}) 3137 (w), 3085 (m), 1644 (m), 1565 (s), 1374 (m), 1100 (w); ^{1}H NMR ($CDCl_3$) δ 3.97 (ABqd, J = 12.5, 6.0 Hz, 2H), 4.56 (dd, J = 12.5, 3.7 Hz, 1H), 4.85 (dd, J = 12.5, 9.5 Hz, 1H), 5.14−5.28 (m, 3H), 5.44−5.80 (m, 1H), 6.38 (m, 1H), 6.42 (m, 1H), 7.45 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 70.0, 70.3, 77.4, 110.0, 110.4, 118.1, 133.4, 143.6, 148.9; MS (DCI, CH_4) *m/e* (rel intensity) 196 ([M − H]$^+$, 14), 153 (23), 140 (39), 123 (22), 110 (56), 97 (100), 94 (87); HRMS calcd for $C_9H_{10}NO_4$ ([M − H]$^+$) 196.0610, found 196.0575.

2-[1-(Allylsulfanyl)-2-nitroethyl]furan (6b). To a stirred solution of allyl mercaptan **2b** (0.659 g, 8.8 mmol) and Et_3N (162 mg, 1.614 mmol) in THF (8 mL) at 0 °C was added a solution of 2-furyl nitroalkene **5** (1.123 g, 8.07 mmol) in THF (6 mL) over 15 min and the reaction mixture was stirred at room temperature overnight (12 h). The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (10 mL) and brine (20 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:9) as eluent to afford pure **6b**. Light yellow oil: yield 1.625 g (94%); IR (film, cm^{-1}) 1644 (m), 1565 (s), 1374 (s), 872 (w); ^{1}H NMR ($CDCl_3$) δ 3.16 (ABqt, J = 12.1, 1.1 Hz, 2H), 4.63 (dd, J = 8.8, 6.6 Hz, 1H), 4.74 (dd, J = 12.8, 6.6 Hz, 1H), 4.87 (dd, J = 12.8, 8.8 Hz, 1H), 5.14−5.23 (m, 2H), 5.70−5.86 (m, 1H), 6.28 (dd, J = 3.3, 0.7 Hz, 1H), 6.34 (dd, J = 3.3, 1.8 Hz, 1H), 7.39 (dd, J = 1.8, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.5, 38.5, 76.7, 108.4, 110.5, 118.4, 133.3, 142.9, 149.5; MS (DCI, isobutane) *m/e* (rel intensity) 213 (M$^+$, 5), 179 (6), 166 (17), 140 (23), 94 (100); HRMS calcd for $C_9H_{11}NO_3S$ (M$^+$) 213.0460, found 213.0474.

2-[1-(Nitromethyl)pent-4-en-1-yl]furan (6c). To a stirred suspension of Mg turnings (0.116 g, 4.8 mmol) and a crystal of iodine in THF (5 mL) was added a solution of 4-bromo-1-butene (0.16 mL) in THF (1 mL). After continued stirring at room temperature for 30 min, additional 4-bromo-1-butene (0.36 mL, total 4.5 mmol) was added dropwise as a solution in THF (2 mL) over 10 min and the reaction mixture was stirred at room temperature for another 1.5 h. The Grignard reagent thus generated was cooled to −78 °C and, with stirring, 2-furyl nitroalkene **5** (0.417 g, 3 mmol) in THF (8 mL) was added over 5 min. The reaction mixture was stirred for another 15 min and then quenched with saturated aqueous NH_4Cl (2.5 mL). It was then brought to room temperature and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography on silica gel using EtOAc/*n*-hexane (1:9) as eluent to afford pure **6c**. Light yellow oil: yield 456 mg (78%); IR (film, cm^{-1}) 3059 (w), 3125 (w), 1637 (m), 1532 (s), 1335 (m); ^{1}H NMR ($CDCl_3$) δ 1.60−2.05 (m, 4H), 3.62 (m, 1H), 4.55 (ABqd, J = 12.0, 7.2 Hz, 2H), 5.00 (m, 2H), 5.72 (m, 1H), 6.14 (m, 1H), 6.30 (m, 1H), 7.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.9, 30.7, 37.2, 78.4, 107.5, 110.2, 115.8, 136.9, 142.2, 152.0; MS (DCI, CH_4) *m/e* (rel intensity) 194 ([M − H]$^+$, 6), 165 (13), 161 (13), 149 (26), 148 (100), 147 (24), 135 (47), 133 (44), 121 (11), 120 (29), 119 (19), 109 (17), 108 (11), 107 (15), 105 (11), 95 (12), 94 (22), 83 (11), 81 (24); HRMS calcd for $C_{10}H_{12}NO_3$ ([M − H]$^+$) 194.0817, found 194.0817.

Diethyl Allyl[1-(2-furyl)-2-nitroethyl]malonate (6d). To a solution of allyl diethylmalonate **2d** (0.354 g, 1.725 mmol) in THF (3 mL), cooled to −20 °C under N_2, was added sodium hydride (83 mg, 60% dispersion in mineral oil, 2.07 mmol) in portions over 10 min and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then cooled to −20 °C and a solution of furyl nitroalkene **5** (0.239 g, 1.725 mmol) in THF (3 mL) was added dropwise during 5 min. The reaction mixture was stirred at 0 °C for 30 min and quenched with saturated aqueous NH_4Cl (2 mL). The reaction mixture was brought to room temperature and extracted with ether (3 × 10 mL). The combined organic layers were washed with water (3 mL) and brine (10 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:4) as eluent to afford pure **6d**. Light yellow oil: yield 353 mg, 61%; IR (film, cm^{-1}) 1729 (s), 1612 (m), 1555 (s), 1381 (m); ^{1}H NMR ($CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 2.36 (dd, J = 14.5, 8.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.33 (X part of ABX, J = 10.1, 3.7 Hz, 1H), 4.94 (B part of ABX, J = 13.6, 10.1 Hz, 1H), 5.01 (A part of ABX, J = 13.6, 3.7 Hz, 1H), 5.15 (m, 2H), 5.72 (m, 1H), 6.23 (m, 1H), 6.29 (m, 1H), 7.34 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.10, 14.11, 38.1, 40.4, 59.4, 62.0, 62.1, 76.4, 110.2, 110.3, 120.0, 131.3, 142.7, 148.4, 168.7, 169.0; MS (DCI, CH_4) *m/e* (rel intensity) 340 (MH$^+$, 48), 294 (26), 293 (83), 292 (53), 251 (28), 247 (33), 220 (22), 219 (100), 218 (61), 201 (25), 191 (26), 177 (27), 173 (32), 145 (28), 94 (93); HRMS calcd for $C_{16}H_{21}NO_7$ (MH$^+$) 340.1396, found 340.1370.

2-[1-(But-3-en-1-yloxy)-2-nitroethyl]furan (6f). To a stirred solution of 3-buten-1-ol **2f** (0.83 g, 11.5 mmol) in THF (10 mL) at −10 to −20 °C was added KOBu^t (1.458 g, 13 mmol) in small portions. After all of the base had dissolved, a solution of 2-furyl nitroalkene **5** (1.39 g, 10 mmol) in THF (10 mL) was added dropwise over 15 min and stirring was continued for another 15 min. The reaction mixture was then quenched with AcOH (2.5 mL) followed by addition of water (10 mL). The reaction mixture was then extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic layers were washed with water (15 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:19) as eluent to afford pure **6f**. Light yellow oil: yield 1.591 g (75.4%); IR (film, cm^{-1}) 3082 (w), 2929 (m), 1649 (w), 1568 (s), 1388 (m), 1107 (m); ^{1}H NMR ($CDCl_3$) δ 2.27 (ABqdd, J = 13.4, 8.5, 2.4 Hz, 2H), 3.45 (dddd, J = 13.4, 8.5, 7.3, 2.4 Hz, 1H), 3.51 (dddd, J = 13.4, 8.5, 7.3, 2.4 Hz, 1H), 4.53 (dd, J = 13.4, 3.7 Hz, 1H), 4.81 (dd, J = 13.4, 9.8 Hz, 1H), 5.01 (m, 2H), 5.11 (dd, J = 9.8, 3.7 Hz, 1H), 5.66−5.80 (m, 1H), 6.38 (m, 1H), 6.42 (m, 1H), 7.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 33.8, 68.9, 71.5, 77.4, 99.1, 109.6, 110.3, 116.5, 134.3, 143.4, 149.0; MS (DCI, CH_4) *m/e* (rel intensity) 210 ([M − H]$^+$, 21), 151 (31), 140 (55), 139 (13), 136 (55), 131 (12), 123 (15), 121 (24), 110 (9), 105 (15), 97 (15), 95 (18), 94 (100), 86 (16), 84 (27), 83 (16); HRMS calcd for $C_{10}H_{12}NO_4$ ([M − H]$^+$) 210.0766, found 210.0777.

Diethyl 2-(But-3-enyl)-2-[1-(furan-2-yl)-2-nitroethyl]-malonate (6g). To a solution of homoallyl diethylmalonate **2g** (309 mg, 1.44 mmol) in dry THF (3 mL), cooled to 0 °C under N_2, was added sodium hydride (42 mg, 60% dispersion in mineral oil, 1.713 mmol) in portions over 5 min. The reaction mixture was stirred at ambient temperature for 30 min. After the reaction mixture was cooled to −20 °C, a solution of 2-furyl nitroalkene **5** (210 mg, 1.516 mmol) in THF (2 mL) was added dropwise over 5 min and stirred at −20 °C for 30 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl (3 mL), brought to room temperature and extracted with ether (3 × 10 mL). The combined ether layers were washed with brine (20 mL), dried (anhyd. Na_2SO_4) and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel by eluting with EtOAc/*n*-hexane (1:15) to afford pure **6g**. Light yellow liquid: yield 366 mg (72%); IR (film, cm^{-1}) 3079 (w), 2983 (m), 1731 (s), 1642 (w), 1559 (s), 1377(m), 1264 (m), 1020 (m); ^1H NMR ($CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.65 (m, 1H), 1.97 (m, 2H), 2.11 (m, 1H), 4.25 (q, J = 7.0 Hz, 2H), 4.28 (q, J = 7.0 Hz, 2H), 4.35 (dd, J = 9.8, 6.7 Hz, 1H), 4.97 (dd, J = 9.8, 4.6 Hz, 2H), 4.92−5.04 (m, 2H), 5.70 (m, 1H), 6.22 (dd, J = 3.4, 0.6 Hz, 1H), 6.29 (dd, J = 3.4, 1.8 Hz, 1H), 7.33 (dd, J = 1.8, 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.89, 13.92, 28.3, 32.9, 40.4, 59.2, 61.9, 62.0, 76.6, 110.0, 110.4, 115.4, 136.8, 142.9, 148.7, 169.1, 169.7; MS (DCI, CH_4) *m/e* (rel intensity) 354 (MH^+, 13), 308 (16), 307 (32), 279 (18), 278 (78), 262 (17), 261 (17), 252 (13), 233 (77), 232 (20), 215 (20), 207 (18), 206 (24), 205 (34), 204 (80), 187 (23), 178 (12), 173 (35), 168 (13), 167 (15), 163 (18), 160 (20), 159 (17), 141 (11), 140 (32), 139 (16), 123 (20), 95 (15), 94 (100); HRMS calcd for $C_{17}H_{24}NO_7$ (MH^+) 354.1552, found 354.1538.

2-[1-(Nitromethyl)hex-5-en-1-yl]furan (6h). To a stirred suspension of Mg turnings (41 mg, 1.7 mmol) and a crystal of iodine in THF (1 mL) was added a solution of 5-bromo-1-pentene (0.075 g, 0.5 mmol) in THF (1 mL). After gentle warming and continued stirring at room temperature for 30 min, additional 5-bromo-1-pentene (0.150 g, 1 mmol) was added dropwise as a solution in THF (2 mL) over 10 min and the reaction mixture was stirred at room temperature for another 1.5 h. The Grignard reagent thus generated was cooled to −78 °C and, with stirring, 2-furyl nitroalkene **5** (0.139 g, 1 mmol) in THF (2 mL) was added over 2 min. The reaction mixture was stirred for another 1 h and then quenched with saturated aqueous NH_4Cl (1 mL). It was then brought to room temperature and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography on silica gel using EtOAc/*n*-hexane (1:19) as eluent to afford pure **6h**. Light yellow liquid: yield 160 mg (76%); IR (film, cm^{-1}) 2930 (m), 2859 (m), 1561 (s), 1382 (m); ^1H NMR ($CDCl_3$) δ 1.3 (quintet, J = 7.5 Hz, 2H), 1.51−1.60 (m, 1H), 1.61−1.71 (m, 1H), 1.89−2.20 (m, 2H), 3.4−3.6 (m, 1H), 4.49 (ABq, J = 12.3 Hz, the high field and low field halves further split into d, J = 7.0 and 7.8 Hz, respectively, 2H), 4.90 (ddd, J = 17.3, 10.2, 1.5 Hz, 2H), 5.68 (m, 1H), 6.0 (d, J = 3.2 Hz, 1H), 6.2 (ABq, J = 3.2, 1.8 Hz, 1H), 7.3 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 30.3, 33.1, 37.8, 78.4, 107.2, 110.2, 115.0, 137.8, 142.1, 152.4; MS (ESI) *m/e* (rel intensity) 208 ($[M - 1]^+$, 70), 194 (15), 105 (20), 77 (68); HRMS calcd for $C_{11}H_{14}NO_3$ ($[M - 1]^+$) 208.0974, found 208.0990.

3-(β-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxy-2-benzofuran (7a) and 3-(α-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxy-2-benzofuran (8a). A solution of the Michael adduct **6a** (0.394 g, 2 mmmol) in toluene (8 mL) was heated under reflux for 4 days. The reaction mixture was then cooled to room temperature and concentrated in vacuo and the crude residue was subjected to column chromatography on silica gel using EtOAc/*n*-hexane (1:4) as eluent to afford pure isomers **7a** and **8a**.

7a: light yellow solid; yield 210 mg (53.3%); mp 45−46 °C; R_f 0.22 (EtOAc/*n*-hexane 1:4); IR (film, cm^{-1}) 1659 (w), 1557 (s), 1380 (m), 1105 (w), 1086 (w); ^1H NMR ($CDCl_3$) δ 1.43 (dd, J = 11.7, 7.3 Hz, 1H), 1.79 (ddd, J = 11.7, 4.0, 2.9 Hz, 1H), 2.30 (dddd, J = 10.3, 8.1, 7.3, 2.9 Hz, 1H), 3.53 (dd, J = 10.3, 8.1 Hz, 1H), 4.20 (t, J = 8.1 Hz, 1H), 4.55 (AB of ABX, J = 7.7 Hz, 2H), 5.07 (X of ABX further split, ddd, J = 7.7, 4.8, 1.1 Hz, 1H), 5.13 (dd, J = 4.0, 1.1 Hz, 1H), 6.46 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.7, 45.4, 73.2, 73.3, 75.0, 81.0, 97.5, 133.1, 137.5; MS (DCI, isobutane) *m/e* (rel intensity) 197 (M^+, 31), 184 (6), 168 (7), 150 (7), 137 (49), 123 (15), 109 (25), 94 (100), 79 (56); HRMS calcd for $C_9H_{11}NO_4$ (M^+) 197.0688, found 197.0669.

8a: off white solid; yield 52 mg (13.2%); mp 127−128 °C; R_f 0.18 (EtOAc/*n*-hexane 1:4); IR (KBr, cm^{-1}) 1656 (w), 1558 (s), 1386 (m), 703 (w); ^1H NMR ($CDCl_3$) δ 0.92 (dd, J = 11.5, 7.6 Hz, 1H), 1.37 (ddd, J = 11.5, 3.4, 2.9 Hz, 1H), 1.83 (dddd, J = 10.2, 8.0, 7.6, 2.9 Hz, 1H), 3.48 (dd, J = 10.2, 8.2 Hz, 1H), 4.00 (dd, J = 12.5, 6.4 Hz, 1H), 4.00 (dd, J = 12.5, 5.3 Hz, 1H), 4.10 (dd, J = 10.2, 8.0 Hz, 1H), 4.78 (d, J = 3.4 Hz, 1H), 4.84 (dd, J = 6.4, 5.3 Hz, 1H), 6.02 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.3, 44.5, 73.5, 74.5, 76.9, 80.4, 98.8, 131.7, 138.1; MS (DCI, isobutane) *m/e* (rel intensity) 199 ($[M + 2]^+$, 17), 198 (MH^+, 30), 190 (9), 181 (33), 169 (83), 163 (8), 151 (24), 137 (100), 131 (31), 125 (21), 119 (30), 109 (99), 95 (42), 80 (21); HRMS calcd for $C_9H_{11}NO_4$ (MH^+) 198.0766, found 198.0729.

3-(β-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxy-2-benzothiophene (7b) and 3-(α-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxy-2-benzothiophene (8b). A solution of the Michael adduct **6b** (0.426 g, 2 mmmol) in toluene (8 mL) was heated under reflux for 4 days. The reaction mixture was then cooled to room temperature and concentrated in vacuo and the crude residue was subjected to column chromatography on silica gel using EtOAc/*n*-hexane (1:4) as eluent to afford pure isomers **7b** and **8b**.

7b: light yellow oil; yield 210 mg (49.5%); R_f 0.28 (EtOAc/*n*-hexane 1:4); IR (film, cm^{-1}) 1662 (m), 1557 (s), 1385 (m), 1048 (m); ^1H NMR ($CDCl_3$) δ 1.47 (dd, J = 11.7, 7.4 Hz, 1H), 1.76 (ddd, J = 11.7, 4.4, 2.5 Hz, 1H), 2.38 (dddd, J = 10.7, 7.4, 7.3, 2.5 Hz, 1H), 2.77 (t, J = 10.7 Hz, 1H), 3.01 (dd, J = 10.7, 7.3 Hz, 1H), 4.50 (m, 2H), 4.75 (dd, J = 17.1, 9.6 Hz, 1H), 5.03 (d, J = 4.4, 1.2 Hz, 1H), 6.36 (ABq, J = 5.7 Hz, the low field half further split into d, J = 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 33.8, 36.8, 42.5, 49.7, 76.1, 80.3, 99.0, 135.3, 137.6; MS (DCI, isobutane) *m/e* (rel intensity) 213 ((M^+, 30), 183 (5); 166 (100), 153 (42), 140 (16), 133 (35), 125 (41), 94 (83), 73 (9); HRMS calcd for $C_9H_{11}NO_3S$ (M^+) 213.0460, found 213.0450.

8b: off white solid: yield 30 mg (7%); mp 92−93 °C; R_f 0.18 (EtOAc/*n*-hexane 1:4); IR (KBr, cm^{-1}) 1665 (m), 1557 (s), 1383 (m), 1050 (m); ^1H NMR ($CDCl_3$) δ 1.56 (dd, J = 12.0, 7.5 Hz, 1H), 1.83 (ddd, J = 12.0, 4.5, 2.5 Hz, 1H), 2.35 (dddd, J = 11.0, 10.5, 7.5, 2.5 Hz, 1H), 2.78 (t, J = 10.5 Hz, 1H), 3.14 (dd, J = 11.0, 10.5 Hz, 1H), 4.30 (dd, J = 7.5, 7.0 Hz, 1H), 4.61 (dd, J = 14.0, 7.0 Hz, 1H), 4.85 (dd, J = 14.0, 7.5 Hz, 1H), 5.07 (dd, J = 4.5, 1.5 Hz, 1H), 6.28 (d, J = 6.0 Hz, 1H), 6.52 (dd, J = 6.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.5, 36.6, 43.8, 47.3, 78.0, 79.4, 100.6, 132.1, 138.9; MS (DCI, isobutane) *m/e* (rel intensity) 213 (M^+, 17), 182 (11), 167 (85), 166 (52), 153 (42), 135 (22), 125 (20), 105 (8), 94 (100); HRMS calcd for $C_9H_{11}NO_3S$ (M^+) 213.0460, found 213.0449. Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.68; H, 5.20; N, 6.57. Found: C, 49.95; H, 5.20; N, 6.60.

Diethyl 3-(β-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxyindene-2,2-dicarboxylate (7d) and Diethyl 3-(α-Nitromethyl)-1,6,7,7a-tetrahydro-3a,6-epoxyindene-2,2-dicarboxylate (8d). A solution of the Michael adduct **6d** (1.290 g, 3.8 mmmol) in toluene (30 mL) was heated under reflux for 2 days. The reaction mixture was then cooled to room temperature and concentrated in vacuo and the crude residue was subjected to column chromatography on silica gel using EtOAc/*n*-hexane (1:4) as eluent to afford pure isomers **7d** and **8d**.

7d: light yellow oil; yield 770 mg (60%); R_f 0.34 (EtOAc/*n*-hexane 1:4); IR (film, cm^{-1}) 2985 (m), 2933 (w), 1741 (s), 1449 (m), 1375 (s), 1242 (s), 1048 (m); ^1H NMR ($CDCl_3$) δ 1.21 (ABq,

J = 7.2 Hz, 6H), 1.48 (dd, J = 11.4, 7.8 Hz, 1H), 1.69 (dt, J = 11.4, 4.2, 3.2 Hz, 1H), 1.87 (dddd, J = 8.8, 8.5, 7.8, 4.2 Hz, 1H), 2.39 (dd, J = 8.8, 8.5 Hz, 2H), 4.10 (t, J = 7.1 Hz, 1H), 4.19 (m, 4H), 4.63 (d, J = 7.1 Hz, 2H), 4.93 (dd, J = 3.2, 1.1 Hz, 1H), 6.21 (dd, J = 5.8, 1.1 Hz, 1H), 6.29 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 13.8, 33.3, 38.2, 40.9, 42.3, 61.7, 62.0, 64.1, 72.4, 79.6, 96.8, 134.9, 136.1, 168.8, 170.9; MS (DCI, isobutane) *m/e* (rel intensity) 340 (MH^+, 18), 293 (41), 252 (16), 220 (100), 201 (44), 145 (35), 117 (23), 94 (48), 79 (18); HRMS calcd for $C_{16}H_{21}NO_7$ (MH^+) 340.1396, found 340.1386.

8d: yellow oil; 135 mg (10.4%); R_f 0.28 (EtOAc/*n*-hexane 1:4); IR (film, cm^{-1}) 2984 (m), 1740 (s), 1449 (w), 1375 (m), 1245 (s), 1049 (s); ^{1}H NMR ($CDCl_3$) δ 1.25 (td, J = 7.1, 3.4 Hz, 6H), 1.42 (dd, J = 11.5, 7.2 Hz, 1H), 1.69 (ddd, J = 11.5, 4.4, 2.8 Hz, 1H), 2.07 (m, 2H), 2.51 (dd, J = 12.8, 6.2 Hz, 1H), 3.50 (dd, J = 9.0, 4.7 Hz, 1H), 4.20 (m, 4 H), 4.90−5.08 (ABq, J = 14.5 Hz, high field half further split d, J = 4.7 Hz, low field half further split d, J = 9.0 Hz, 2H), 5.00 (dd, J = 4.4, 1.6 Hz, 1H), 6.29 (dd, J = 5.9, 1.6 Hz, 1H), 6.40 (d, J = 5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 31.6, 39.1, 43.2, 44.5, 62.1, 66.5, 74.2, 80.2, 98.2, 133.5, 136.4, 169.7, 170.4; MS (DCI, CH_4) *m/e* (rel intensity) 339 (M^+, 18), 293 (39), 292 (12), 251 (19), 247 (11), 220 (22), 219 (100), 218 (55), 201 (33), 192 (27), 173 (11), 145 (10), 94 (16); HRMS calcd for $C_{16}H_{21}NO_7$ (M^+) 339.1318, found 339.1260.

2-Allyl-3-(β-nitromethyl)-1,2,3,6,7,7a-hexahydro-3a,6-epoxyisoindole (7e) and 2-Allyl-3-(α-nitromethyl)-1,2,3,6,7,-7a-hexahydro-3a,6-epoxyisoindole (8e). A solution of diallylamine **2e** (0.32 g, 3.3 mmol), 2-furyl nitroalkene **5** (0.417 g, 3 mmol) and THF (15 mL) was heated under reflux for 7 days. The reaction mixture was cooled and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel by eluting with EtOAc/*n*-hexane (1:1) to afford **7e** and **8e** as an inseparable mixture of isomers. Brown oil: yield 320 mg (45%; 27% of **5** was recovered), inseparable mixture of isomers (83:17); R_f 0.27 (EtOAc/*n*-hexane 1:3); IR (film, cm^{-1}) 2939 (s), 1671 (m), 1558 (s), 1380 (m), 1100 (m), 943 (m); ^{1}H NMR ($CDCl_3$) δ 1.27 (dd, J = 12.2, 7.3 Hz, 1H), 1.57−1.66 (m, 1H), 1.91−1.97 (m, 1H), 2.14 (dd, J = 9.8, 8.5 Hz, 1H), 3.12−3.22 (m, 2H), 3.29 (dd, J = 8.5, 6.1 Hz, 1H), 3.36 (t, J = 4.9 Hz, 1H), 4.54 (d, J = 4.9 Hz, 2H), 4.90 (d, J = 4.9 Hz, 1H), 5.05 (d, J = 9.8 Hz, 1H), 5.13 (dd, J = 17.1, 7.3 Hz, 1H), 5.69−5.83 (m, 1H), 6.27 (d, J = 6.1 Hz, 1H), 6.38 (d, J = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (M = major isomer, m = minor isomer) 30.2 (M), 31.4 (m), 41.5 (M), 42.6 (m), 57.3 (m), 57.7 (M), 58.6 (M), 59.0 (m), 60.7 (m), 61.9 (M), 75.0 (m), 76.5 (M), 79.5 (M), 80.1 (m), 96.1 (M), 98.2 (m), 117.6 (M and m), 133.2 (M), 134.7 (m), 135.0 (M), 135.2 (m), 136.3 (m), 136.6 (M); MS (DCI, CH_4) *m/e* (rel intensity) 236 (M^+, 13), 189 (13), 177 (11), 176 (100), 169 (12), 119 (13); HRMS calcd for $C_{12}H_{16}N_2O_3$ (M^+) 236.1161, found 236.1162.

1-(β-Nitromethyl)-4,4a,5,6-tetrahydro-3*H*-6,8a-epoxyisochromene (7f). A solution of the Michael adduct **6f** (1.36 g, 6.45 mmmol) in mesitylene (60 mL) was heated at 150 °C for 3 days. The reaction mixture was then cooled to room temperature and concentrated in vacuo and the crude residue (single isomer from ^{1}H NMR, 400 MHz) was subjected to column chromatography on silica gel using EtOAc/*n*-hexane (1:4) as eluent to afford pure **7f**. Colorless oil: yield 800 mg (59%; 32% of **6f** was recovered); R_f 0.28 (EtOAc/*n*-hexane 1:4); IR (KBr, cm^{-1}) 2948 (m), 2926 (m), 1559 (s), 1384 (m), 1217 (s), 1089 (w); ^{1}H NMR ($CDCl_3$) δ 1.48−1.65 (m, 3H), 1.77 (ddd, J = 14.7, 7.3, 3.7 Hz, 1H), 1.87 (ddd, J = 13.4, 6.1, 3.7 Hz, 1H), 3.52 (ddd, J = 14.7, 12.2, 2.4 Hz, 1H), 4.00 (ddd, J = 12.2, 3.7, 2.4 Hz, 1H), 4.45 (dd, J = 13.4, 2.4 Hz, 1H), 4.64 (dd, J = 13.4, 9.8 Hz, 1H), 4.76 (dd, J = 9.8, 2.4 Hz, 1H), 5.01 (d, J = 2.4 Hz, 1H), 6.20 (ABq, J = 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.7, 31.1, 34.06, 34.11, 67.0, 74.2, 79.4, 84.3, 133.1, 138.8; MS (DCI, isobutane) *m/e* (rel intensity) 212 (MH^+, 63), 181 (56), 151 (100), 136 (78), 121 (76), 119 (65), 94 (81); HRMS calcd for $C_{10}H_{14}NO_4$ (MH^+) 212.0923, found 212.0916.

Diethyl 5-(β-Nitromethyl)-1,7,8,8a-tetrahydro-2*H*-2,4a-epoxynaphthalene-6,6-dicarboxylate (7g). A solution of the Michael adduct **6g** (0.112 g, 0.317 mmol) in xylene (20 mL) was heated under reflux for 3 days. The reaction mixture was then cooled to room temperature and concentrated in vacuo and the crude residue (single isomer from ^{1}H NMR, 400 MHz) was subjected to column chromatography on silica gel using EtOAc/*n*-hexane (1:8) as eluent to provide pure **7g**. Light yellow oil: yield 82 mg (73%); R_f 0.7 (EtOAc/*n*-hexane 1:8); IR (film, cm^{-1}) 2972 (m), 2930 (m), 1733 (s), 1650 (w), 1555 (s), 1452 (m), 1377 (m), 1232 (m), 1025 (m); ^{1}H NMR ($CDCl_3$) δ 1.23 (ABq, J = 7 Hz, 3H), 1.24 (ABq, J = 7 Hz, 3H), 1.38−1.42 (m, 1H), 1.49−1.56 (m, 2H), 1.59−1.73 (m, 1H), 1.82 (tdd, J = 13.4, 3.4, 0.9 Hz, 1H), 1.93 (ddd, J = 13.4, 13.1, 5.5 Hz, 1H), 2.48 (ddd, J = 14.1, 13.4, 3.4 Hz, 1H), 3.80 (dd, J = 6.4, 6.1 Hz, 1H), 4.20 (ABqq, J = 15.9, 7.0 Hz, 4H), 4.90 (dddd, J = 15.9, 6.4, 6.1, 1.2 Hz, 2H), 4.91 (dd, J = 2.7, 1.2 Hz, 1H), 5.93 (d, J = 5.5 Hz, 1H), 6.36 (dt, J = 5.5, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (x 2), 27.4, 32.6, 35.0, 35.9, 40.7, 56.3, 61.5, 62.3, 75.4, 78.9, 87.6, 134.6, 138.6, 169.0, 171.2; MS (DCI, CH_4) *m/e* (rel intensity) 354 (MH^+, 19), 307 (53), 279 (20), 278 (100), 277 (34), 261 (11), 249 (12), 234 (14), 233 (72), 232 (12), 215 (23), 207 (11), 206 (19), 205 (37), 204 (92), 203 (11), 187 (22), 173 (42), 163 (11), 159 (14), 131 (11), 105 (25), 94 (65); HRMS calcd for $C_{17}H_{24}NO_7$ (MH^+) 354.1553, found 354.1558.

5-(β-Nitromethyl)-1,7,8,8a-tetrahydro-2*H*-2,4a-epoxynaphthalene (7h). A solution of the Michael adduct **6h** (0.108 mg, 0.51 mmol) in mesitylene (10 mL) was maintained at 140−145 °C for 60 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:19) as eluent to afford pure **7h**. Yellow oil: yield 20 mg (18%); R_f 0.46 (EtOAc/*n*-hexane 1:4); IR (film, cm^{-1}) 2925 (s), 2854 (m), 1546 (s), 1388 (m); ^{1}H NMR ($CDCl_3$) δ 1.30−1.50 (m, 4H), 1.50−1.62 (m, 2H), 1.71−1.82 (m, 2H), 1.90−2.00 (ddd, J = 13.5, 4.8, 2.6 Hz, 1H), 2.8−3.0 (m, 1H), 4.3 (dd, J = 12.6, 9.5 Hz, 1H), 4.55 (dd, J = 12.6, 4.2 Hz, 1H), 4.9 (ABq, J = 4.6, 1.6 Hz, 1H), 6.0 (d, J = 5.5 Hz, 1H), 6.37 (ABq, J = 5.5, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.4, 31.7, 35.3, 35.7, 38.3, 78.5, 78.9, 86.9, 135.5, 138.4; MS (ESI) *m/e* (rel intensity) 232 ($[M + Na]^+$, 30), 183 (70), 145 (100), 123 (15); HRMS calcd for $C_{11}H_{15}NO_3Na$ ($[M + Na]^+$) 232.0950, found 232.0941.

1-(β-Nitromethyl)-4,4a,5,6-tetrahydro-3*H*-6,8a,7,8-diepoxyisochromene (13). To a solution of *m*-CPBA (0.57 g, 50%, 1.658 mmol) in CH_2Cl_2 (5 mL), cooled to 0 °C, was added dropwise a solution of **7f** (0.35 g, 1.658 mmol) in CH_2Cl_2 (3 mL) over 3 min. The reaction mixture was stirred at room temperature for 2 h and then diluted with cold 4% aq sodium bicarbonate solution (4 mL). The organic layer was separated, washed with water (10 mL) and concentrated in vacuo. The crude residue (single isomer by ^{1}H NMR, 400 MHz) was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:5) as eluent to provide pure epoxide **9**. Off white crystals (1:1 ether/DCM): yield 295 mg (78.3%); R_f 0.13 (EtOAc/*n*-hexane 1:4); mp 116−118 °C; IR (KBr, cm^{-1}) 2950 (w), 2924 (w), 1559 (s), 1382 (m), 1093 (m), 910 (s), 737 (m); ^{1}H NMR ($CDCl_3$) δ 1.48−1.61 (m, 2H), 1.74−1.82 (m, 2H), 1.94−2.02 (m, 1H), 3.21 (d, J = 3.6 Hz, 1H), 3.36 (d, J = 3.6 Hz, 1H), 3.43 (ddd, J = 12.5, 11.9, 1.5 Hz, 1H), 3.95 (ddd, J = 11.9, 4.3, 1.5 Hz, 1H), 4.55 (d, J = 4.9 Hz, 1H), 4.61−4.70 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 30.5, 35.3, 36.6, 50.5, 51.1, 66.6, 73.6, 74.8, 76.3, 79.4; MS (DCI, CH_4) *m/e* (rel intensity) 228 (M^+, 9), 209 (11), 207 (23), 206 (18), 205 (22), 189 (59), 181 (80), 180 (58), 179 (22), 177 (24), 163 (22), 161 (37), 151 (36), 139 (38), 137 (31), 135 (45), 133 (34), 125 (20), 123 (39), 121 (23), 111 (46), 109 (100), 107 (44), 105 (41); HRMS calcd for $C_{10}H_{14}NO_5$ (M^+) 228.0872, found 228.0855.

3a,4-Dihydro-1-(nitromethyl)isobenzofuran-5-(1*H*,3*H*,6*H*)-one (14). To a solution of **7a** (197 mg, 1 mmol) in dry CH_2Cl_2 (5 mL) cooled to −78 °C under N_2 was added $BF_3{\cdot}Et_2O$ (0.27 mL, tech 50%, 1.1 mmol) in CH_2Cl_2 (5 mL) over 3 min. After being stirred at the same temperature for 15 min,

the reaction mixture was warmed to 0 °C over a period of 3 h. The cooling bath was removed and the reaction mixture was stirred at room temperature for another 4 h. The reaction mixture was then diluted with water (5 mL) and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (10 mL) and the combined organic layers were washed with water (2 × 4 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude residue was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:4) as eluent to provide pure **14**. Light yellow oil: yield 120 mg (51%); R_f 0.26 (EtOAc/pet. ether 1:3); IR (KBr, cm^{-1}) 3057 (w), 1707 (br, s), 1557 (m), 1378 (w), 1266 (s), 740 (s), 702 (w); ^1H NMR ($CDCl_3$) δ 2.17 (dd, J = 14.7, 12.2 Hz, 1H), 2.68 (dd, J = 14.7, 5.4 Hz, 1H), 2.84−3.22 (m, 3H), 3.51 (dd, J = 9.8, 8.4 Hz, 1H), 4.28 (t, J = 8.4 Hz, 1H), 4.50 (m, 2H), 5.21 (m, 1H), 5.73 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 38.4, 40.2, 41.5, 72.5, 75.8, 77.7, 116.5, 141.2, 207.5; MS (DCI, CH_4) *m/e* (rel intensity) 197 (M^+, 14), 179 (32), 150 (40), 137 (33), 94 (53), 69 (100); HRMS calcd for $C_9H_{11}NO_4$ (M^+) 197.0688, found 197.0650.

1,3,3a,4,5,6-Hexahydro-1-(nitromethyl)isobenzofuran-5,6-diacetate (15). To a solution of **7a** (210 mg, 1.07 mmol) in acetic anhydride (2 mL) was added concentrated H_2SO_4 (0.2 mL) and the resulting mixture was stirred at room temperature for 8 h. The light brown reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with water (2 × 4 mL) and brine (10 mL), dried (anhyd Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel column chromatography using EtOAc/*n*-hexane (1:4) as eluent to provide **15** as a mixture of two isomers (~3:1, ^1H NMR). Light brown oil: yield 230 mg (73%).

The isomeric mixture **15** was dissolved in ether (6 mL) and the precipitated solid was filtered. The solid was recrystallized from Et_2O/CH_2Cl_2 (1:1) to provide pure **15a.** The mother liquors were combined and concentrated in vacuo. The residue was again subjected to column chromatography using EtOAc/*n*-hexane (1:4) as eluent to provide crude **15b**. It was crystallized from ether (~2 mL) to provide pure **15b**.

1,3,3a,4,5,6-Hexahydro-1-(nitromethyl)isobenzofuran-*cis*-5,6-diacetate (15a). Colorless crystalline solid: yield 110 mg (35%); R_f 0.53 (EtOAc/pet. ether 1:3); mp 163−165 °C; IR (KBr, cm^{-1}): 3055 (s), 2987 (m), 2865 (w), 1740 (s), 1559 (s), 1422 (m), 1374 (m), 1266 (s), 1031 (m), 897 (m); ^1H NMR (C_6D_6/$CDCl_3$ 4:1) δ 0.90 (dd, J = 12.0, 11.8 Hz, 1H), 1.69 (ddd, J = 11.8, 3.9, 3.5 Hz, 1H), 1.73 (s, 3H), 1.77 (s, 3H), 2.24 (ddd, J = 12.2, 10.7, 10.2 Hz, 1H), 2.71 (dd, J = 10.7, 8.2 Hz, 1H), 3.48 (dd, J = 13.1, 2.9 Hz, 1H), 3.51 (dd, J = 10.2, 8.2 Hz, 1H), 3.66 (dd, J = 13.1, 9.1 Hz, 1H), 4.73 (dd, J = 9.1, 2.9 Hz, 1H), 4.92 (dd, J = 5.1, 2.7 Hz, 1H), 5.10 (ddd, J = 12.2, 12.0, 3.9 Hz, 1H), 5.46 (ddd, J = 12.2, 5.1, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.0, 30.1, 40.1, 71.3, 71.8, 72.4, 75.0, 77.4, 117.0, 145.0, 170.4, 170.8; MS (DCI, CH_4) *m/e* (rel intensity) 240 ($[M - OAc]^+$, 62), 197 (42), 179 (44), 150 (100); HRMS calcd for $C_{11}H_{14}NO_5$ ($[M - OAc]^+$) 240.0872, found 240.0861. Anal. Calcd for $C_{13}H_{17}NO_7$: C, 52.17; H, 5.73; N, 4.68. Found: C, 51.27; H, 5.74; N 4.69.

1,3,3a,4,5,6-Hexahydro-1-(nitromethyl)isobenzofuran-*trans*-5,6-diacetate (15b). Off white needles: yield 46 mg (14%); R_f 0.46 (EtOAc/pet. ether 1:3); mp 105−107 °C; IR (KBr, cm^{-1}) 3055 (s), 2987 (m), 2876 (w), 1743 (s), 1559 (s), 1422 (m), 1371 (m), 1266 (s), 1071 (w); ^1H NMR (C_6D_6/$CDCl_3$ 4:1) δ 1.26 (2 × ABq, J = 11.6 Hz, 1H), 1.46 (ddd, J = 11.6, 5.3, 3.6 Hz, 1H), 1.67 (s, 3H), 1.80 (s, 3H), 2.20 (unresolved m, 1H), 2.86 (dd, J = 10.9, 8.3 Hz, 1H), 3.63 (dd, J = 10.9, 8.1 Hz, 1H), 3.66 (dd, J = 13.0, 7.8 Hz, 1H), 3.74 (dd, J = 13.0, 8.8 Hz, 1H), 4.73 (dd, J = 8.8, 7.8 Hz, 1H), 4.79 (dt, J = 11.6, 3.6 Hz, 1H), 4.93 (dd, J = 4.1, 2.1 Hz, 1H), 5.49 (dd, J = 4.1, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 20.9, 25.4, 41.0, 64.4, 69.3, 71.2, 74.9, 77.4, 116.1, 145.8, 170.0, 170.2; MS (DCI, CH_4) *m/e* (rel intensity) 240 ($[M - OAc]^+$, 48) 197 (44), 192 (30), 179 (70), 150 (100); HRMS calcd for $C_{11}H_{14}NO_5$ ($[M - OAc]^+$) 240.0872, found 240.0902.

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Supporting Information Available: X-ray data for **8b**, **13** and **15a** in CIF format, copies of ^1H and ^{13}C NMR spectra for all new compounds, and tables of NMR (^1H, ^{13}C, 2D-COSY and NOESY) data for **7a**−**e** and **8a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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