Thermal Isomerization of 1,3-Dipolar Cycloadducts of 3,4-Dihydro-β-carboline 2-Oxide

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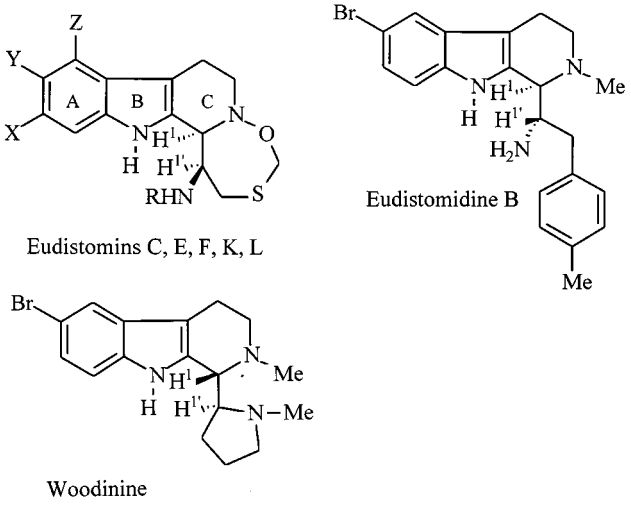
The thermal isomerization of the 1,3-dipolar cycloadducts of 3,4-dihydro-β-carboline 2-oxide is studied using ^{1}H-NMR spectroscopy. Stereoisomerizations of the *cis* or *syn* cycloadducts with dipolarophiles such as methyl crotonate, methyl cinnamate, and methyl methacrylate into the *trans* or *anti* cycloadducts are observed. On the other hand, regioisomerization of the 1-substituted cycloadduct with nitroethylene into the 2-substituted cycloadduct is also observed.

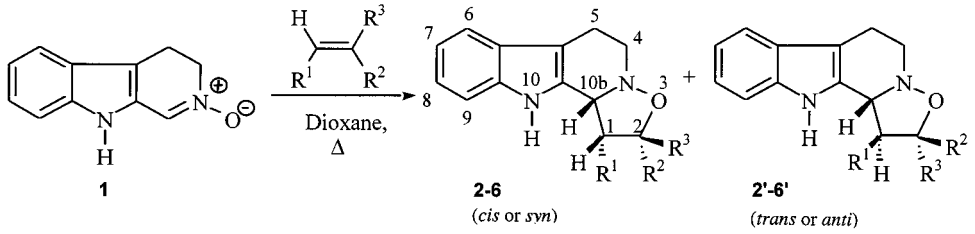
Introduction

The 1,3-dipolar cycloaddition reaction of nitrones is a useful method for construction of fused heterocycles[1][2] and has been applied to the synthesis of natural products.[3][4][5] Recently, we reported the 1,3-dipolar cycloaddition reaction of 3,4-dihydro-β-carboline 2-oxide **1** with a variety of dipolarophiles and stated an understanding concerning its regio- and stereoselectivity (see Scheme 1).[6] This 1,3-dipolar cycloaddition reaction may play an important role for the synthesis of β-carboline derivatives which have biological and pharmaceutical properties,[7] such as eudistomins[8][9] and eudistomidines.[10][11] Particularly, in β-carboline compounds, the stereochemical relationship between 1-H in the β-carboline ring and 1′-H in the 1,2-fused ring (D ring) or in the substitution group in 1-position has a great influence on the biological activity (Figure 1). For example, in eudistomins C, E, F, K, and L, *cis* configuration between the protons 1-H and 1′-H is an indispensable factor for antiviral and antitumor activity,[12] while in eudistomidine B[11] and woodinine,[13] *trans* configuration between them is essential. It is thus probable that 1,3-dipolar cycloadducts will be useful in the synthesis of pharmaceutical compounds, only if they fulfil these stereo-

Figure 1. The bioactive β-carboline compounds



Scheme 1



2, **2'** : R^1 = COOMe, R^2 = H, R^3 = Me ; **3**, **3'** : R^1 = COOMe, R^2 = H, R^3 = Ph ;
4, **4'** : R^1 = COOMe, R^2 = H, R^3 = COOMe ;
5, **5'** : R^1 = COOMe, R^2 = COOMe, R^3 = H ; **6**, **6'** : R^1 = H, R^2 = COOMe, R^3 = Me

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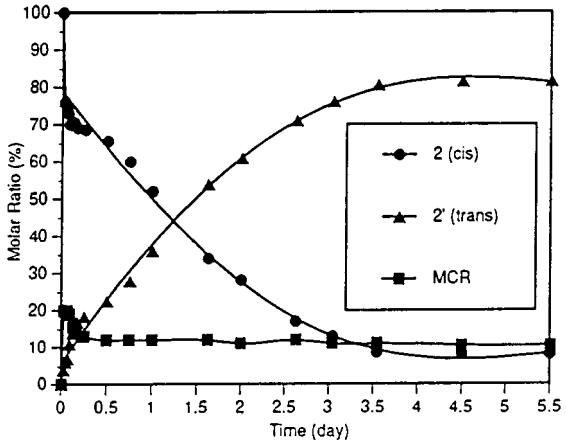
chemical requirements. However, it is difficult to find a general rule for the stereoselectivity in 1,3-dipolar cycloaddition reactions of nitrones,[1] as isomerization often occurs through retro 1,3-dipolar reaction.[14] For example, it was recently reported that the *cis* 1,3-dipolar cycloadduct of 3,4-dihydroisoquinoline *N*-oxide with methyl crotonate isomerizes into its stereoisomer, the *trans* cycloadduct, by heating at 80°C for 1 day.[15] As part of a study on the stereoselectivity of 1,3-dipolar cycloaddition reactions, we were interested in thermal isomerization of the 1,3-dipolar cycloadducts of **1**. Our goal in this investigation is not only to understand the stereoselectivity rules governing these 1,3-dipolar cycloaddition reaction, but also to use the isomerization for stereoselective synthesis. In this paper, we report thermal stereo-isomerization between *cis* and *trans* 1,3-dipolar cycloadducts of **1** and between *syn* and *anti* cycloadducts.[16] Thermal regioisomerization between 1-substituted and 2-substituted cycloadducts is also reported.

Results and Discussion

The 1,3-dipolar cycloaddition reaction of **1** with methyl crotonate (ca. 3 equiv.) at 100°C for 2 h gives *cis* and *trans* cycloadducts, **2** and **2′**, with respect to 1-H and 10b-H, in the ratio 85:15 and 85% yield. We described in a previous paper[6] that the reaction with methyl crotonate shows *cis* selectivity due to secondary orbital interaction between orbitals at C-4a and C-9a in **1** and orbitals of the carbonyl group in the dipolarophiles. On the other hand, when the same reaction was run at 100°C for 3 days, the reverse *trans* selectivity was obtained (**2**/**2′** = 9:91, yield = 70%). Although both cycloadducts **2** and **2′** can be isolated and are stable at room temperature, isomerization between **2** and **2′** might occur during long heating time. To clear up this reversal of stereoselectivity, we investigated the thermal isomerization of the 1,3-dipolar cycloadducts of **1**. The isolated cycloadduct **2** was heated at 100°C in [D_8]dioxane in an NMR tube and the conversions with the passage of time were observed using ^{1}H-NMR (300 MHz) analysis. The molar ratios of **2**, **2′**, and methyl crotonate were calculated by integration values of the methyl protons in **2** (δ = 1.33), **2′** (δ = 1.27), and methyl crotonate (δ = 1.82). Results are summarized in Figure 2. In the initial state, methyl crotonate (MCR) and nitrone **1** (δ = 7.62, olefinic proton; δ = 9.78, NH proton) were generated in about 20% molar ratio each and the *cis* cycloadduct **2′** decreased by the corresponding portion to about 80% molar ratio. After that, the quantity of *cis* cycloadduct **2** gradually decreased, while the *trans* cycloadduct **2′** formed, and methyl crotonate maintained around 11% molar ratio. Finally, the system, **2**, **2′**, and methyl crotonate reached equilibrium at a 8:81:11 molar ratio. This ratio is in accord with the isolated ratio (**2**/**2′** = 9:91). On the other hand, heating the *trans* adduct **2′** at 100°C also generated methyl crotonate and **1** through retro 1,3-dipolar reaction, but the cycloconversion of **2′** into **2** was limited to a small amount. Finally, after 2 days, **2**, **2′**, and methyl crotonate reached equilibrium at the same molar ratio as was obtained starting from **2** (Entry 2 in Table 1). These experiments proved that the isomerization mainly proceeded from the *cis* cycloadduct **2** to the *trans* cycloadduct **2′** through retro 1,3-dipolar cycloaddition reaction under thermal conditions (Scheme 2). The results of the thermal isomerization indicate that the *cis* 1,3-dipolar cycloadduct **2** is the product resulting from kinetic control, and that the *trans* 1,3-dipolar cycloadduct **2′** is the product obtained under thermodynamic conditions.

Figure 2. Isomerization of **2** in [D_8]dioxane at 100°C



The reaction of **1** with the bulkier methyl cinnamate gives low yield (32%, for 1 day at 100°C) and poor stereoselectivity (**3**/**3′** = 45:55). This result might be related to thermal isomerization. When the *cis* adduct **3** was heated at 100°C for 1 h, complete retro 1,3-dipolar reaction was observed giving only methyl cinnamate and **1** in the system (Entry 3). On prolonged heating, the *trans* adduct **3′** gradually formed as well as a small amount of the *cis* cycloadduct **3**. Finally, the system reached equilibrium with the ratio, **3**/**3′**/methyl cinnamate = 5:32:63 (Entry 4). Heating the *trans* adduct **3′** for 1 day gave the same equilibrium state (Entry 5). The molar ratio of the dipolarophile (methyl cinnamate)

Scheme 2

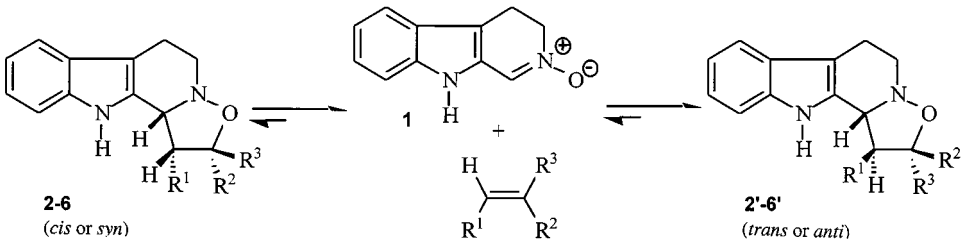


Table 1. Isomerization of the 1,3-dipolar cycloadducts at 100°C

Entry	R^1	R^2	R^3	Starting material		Time [d]	*cis* (*syn*)	Molar ratio *trans* (*anti*)	[%] Dipolarophile
1	COOMe	H	Me	**2**	(*cis*)	3.5	8	81	11
2	COOMe	H	Me	**2′**	(*trans*)	2	8	81	11
3	COOMe	H	Ph	**3**	(*cis*)	1 h	0	0	100
4	COOMe	H	Ph	**3**	(*cis*)	3	5	32	63
5	COOMe	H	Ph	**3′**	(*trans*)	2	5	32	63
6	COOMe	H	COOMe	**4**	(*cis*)	3	80	16	4
7	COOMe	COOMe	H	**5**	(*cis*)	3	94	0	6
8	H	COOMe	Me	**6**	(*syn*)	8	34	53	12
9	H	COOMe	Me	**6′**	(*anti*)	3	35	53	11

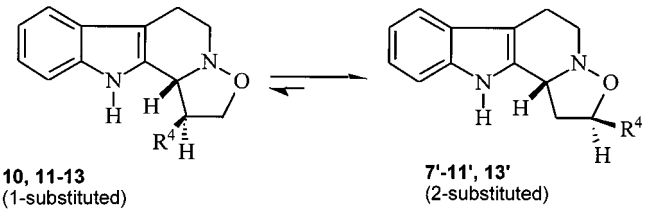
in the equilibrium state showed a high value (63 mol-%), especially when compared with the molar ratio (11 mol-%) of methyl crotonate in the equilibrium state resulting from **2** and **2′**. This indicates that the system favours the retro 1,3-dipolar reaction over the cycloaddition reaction: the isomerization easily occurs. This can explain the low yield and the poor stereoselectivity previously reported.

The reactions of **1** with dimethyl fumarate and maleate also showed *cis* selectivity (**4**/**4′** = 95:5, only **5**) but on prolonged heating of the reactions, the stereoselectivity did not change (after 3 days, **4**/**4′** = 87:13, only **5**). Thermal isomerization of the isolated *cis* adduct **4** was very slow and even after 3 days at 100°C, only a small conversion into **4′** was detected (**4**/**4′**/dimethyl fumarate = 80:16:4, Entry 6). Heating of **5** gave only dimethyl maleate and **1** in a 6% molar ratio and no isomerization was observed (Entry 7). The molar ratios of the dipolarophiles in the equilibrium state obtained from **4** and **5** showed comparatively low values (4 and 6 mol-%). This indicates that these cycloadducts, **4** and **5**, are stable against thermal isomerization.

The reaction with a 1,1-disubstituted dipolarophile such as methyl methacrylate gives *syn* and *anti* cycloadducts (**6**/**6′** = 88:12) and shows *syn* selectively due to secondary orbital interaction between an orbital of the nitrogen atom of the nitrone group present in **1** and an orbital of the oxygen atom of the carbonyl group of the dipolarophile.[17] Heating the isolated *syn* cycloadduct **6** led to its isomerization into the *anti* adduct **6′** and finally afforded a 34:53:12 molar ratio in the equilibrium state (Entry 8). Also, heating the *anti* cycloadduct **6′** afforded a similar molar ratio in the equilibrium state. These results indicate that the *syn* 1,3-dipolar cycloadduct **6** is the product resulting from kinetic control, and that the *anti* 1,3-dipolar cycloadduct **6′** is the product obtained under thermodynamic conditions. These results are comparative to those obtained with the *cis* cycloadduct **2** and the *trans* cycloadduct **2′**.

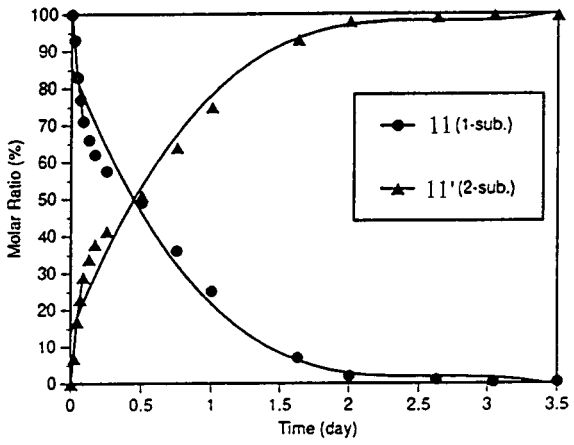
Concerning monosubstituted dipolarophiles, the reactions with styrene, 1-hexene, ethyl vinyl ether, and methyl acrylate give mainly the corresponding 2-substituted *anti* cycloadduct **7′** (yield = 85%), **8′** (73%), **9′** (79%), and **10′** (78%, **10′**/its regioisomer **10** = 95:5) (Scheme 3). We observed that the cycloadducts **7′**, **8′**, and **9′** are stable when heated at 100°C. The cycloadduct **10′** when heated only generated a small amount of **1** and the dipolarophile (methyl acrylate 4 mol-%). However, the 1-substituted cycloadduct **11** obtained regioselectively from the reaction of **1** with nitroethylene (89%),[18] isomerized into its regioisomer, the 2-substituted cycloadduct **11′** by heating at 100°C. The changes of **11** and **11′** with the passage of time are shown in Figure 3. In this case, the dipolarophile (nitroethylene) was not observed in the system and the 1-substituted cycloadduct **11** directly converted into the 2-substituted one **11′**. Finally, the complete isomerization from **11** into **11′** proceeded and reversal of the regioselectivity was observed after 2 days. Unfortunately, the formed cycloadduct **11′** was unstable on silica gel and could not be isolated. Like the reaction with nitroethylene, the reaction with phenyl vinyl sulfone gives the 1-substituted cycloadduct **12** (74%), but no thermal isomerization of **12** was observed.

Scheme 3



7′ : R^4 = Ph ; **8′** : R^4 = *n*-C_4H_9 ; **9′** : R^4 = OEt ; **10**, **10′** : R^4 = COOMe ; **11**, **11′** : R^4 = NO_2 ; **12** : R^4 = SO_2Ph ; **13**, **13′** : R^4 = CN

Figure 3. Isomerization of **11** in [D_8]dioxane at 100°C



The reaction with acrylonitrile gives the 1-substituted and 2-substituted cycloadducts, **13** and **13′** (**13**/**13′** = 77:23, 81%). Heating of **13** showed isomerization into **13′**, and the system **13**/**13′**/acrylonitrile reached equilibrium at a 64:22:14 molar ratio after 3 days. The regiochemical conversion was limited to a lesser amount than that observed in the case of **11**. 1-Substituted cycloadducts are more congested than 2-substituted cycloadducts in the neighbourhood of the substituted group, and the non-bonding steric hindrance around this group may be responsible for the driving force for the regiochemical conversion. The driving force should be influenced by the bulkiness of the substituted group, and indeed, in the case of the less bulky cyano group (compared to the nitro group),[19] the ratio of the conversion into the 2-substituted cycloadduct was lower. Similarly to the above-mentioned stereoisomerization, these results show that in certain case, the 1-substituted cycloadduct is the product resulting from kinetic control, and that the 2-substituted cycloadduct is the product obtained under thermodynamic conditions.

We thank Dr. *Janice Byrne* for helpful advice.

Experimental Section

^{1}H-NMR spectra of the isomerizations were measured in [D_8]1,4-dioxane (99 atom-% D, Acros) using a Bruker AM 300 spectrometer. The signal of 1,4-dioxane (δ = 3.52) was used as internal standard. ^{1}H NMR (300 or 400 MHz, $CDCl_3$/TMS, *J* in Hz), ^{13}C NMR (75 MHz, $CDCl_3$ or DMSO/TMS), IR (KBr), and MS (70 eV) spectral data of all the compounds except **11′** have been reported previously.[6]

Isomerization of the Cycloadducts: The *cis* cycloadduct **2** (10 mg) in [D_8]1,4-dioxane (0.75 ml) in a 5-mm NMR tube was heated in an oil bath at 100°C. ^{1}H-NMR spectra were measured with passage of time and molar ratios of the cycloadducts and the dipolarophile were calculated from integration values of the ^{1}H-NMR spectra.

The cis Cycloadduct **2**: ^{1}H NMR ([D_8]1,4-dioxane): δ = 1.33 (3 H, d, *J* = 6.2, 2-Me), 2.71−2.88 (2 H, m), 3.15−3.24 (2 H, m), 3.52 (3 H, s, 1-OMe), 3.54−3.61 (1 H, m), 4.81−4.91 (2 H, m, 2-H and 10b-H), 6.97 (1 H, br. dd, *J* = 7.0 and 7.9), 7.05 (1 H, br. dd, *J* = 7.0 and 7.9), 7.21 (1 H, br. d, *J* = 7.9), 7.42 (1 H, br. d, *J* = 7.9), 9.35 (1 H, br. s, 10-H).

The trans Cycloadduct **2′**: ^{1}H NMR ([D_8]1,4-dioxane): δ = 1.27 (3 H, d, *J* = 6.1, 2-Me), 2.59−2.68 (1 H, m), 2.78−2.91 (1 H, m), 3.01 (1 H, dd, *J* = 4.9 and 8.5, 1-H), 3.06−3.17 (1 H, m), 3.54−3.63 (1 H, m), 3.76 (3 H, s, 1-OMe), 4.18 (1 H, dq, *J* = 6.1, 8.5, 2-H), 4.93 (1 H, br. d, *J* = 4.9, 10b-H), 6.93−7.07 (2 H, m), 7.23 (1 H, br. d, *J* = 7.3), 7.41 (1 H, br. d, *J* = 7.3), 9.36 (1 H, br. s, 10-H).

3: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.82−2.93 (2 H, m), 3.26−3.55 (1 H, m), 3.30 (3 H, s, 1-OMe), 3.58 (1 H, dd, *J* = 7.3 and 9.8, 1-H), 3.64−3.78 (1 H, m), 5.13 (1 H, br. s, 10b-H), 5.78 (1 H, d, *J* = 7.3, 2-H), 6.98 (1 H, ddd, *J* = 1.2, 7.0, and 7.3), 7.24 (1 H, br. d, *J* = 7.3), 7.29−7.48 (7 H, m), 9.48 (1 H, br. s, 10-H).

3′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.63−2.74 (1 H, m), 2.92−3.04 (1 H, m), 3.22 (1 H, ddd, *J* = 4.9, 8.5, and 13.4), 3.45 (1 H, dd, *J* = 4.9 and 7.3, 1-H), 3.63 (1 H, ddd, *J* = 3.7, 4.9, and 13.4), 3.76 (3 H, s, 1-OMe), 5.08 (1 H, br. d, *J* = 4.9, 10b-H), 5.19 (1 H, d, *J* = 7.3, 2-H), 6.98−7.09 (2 H, m), 7.12−7.20 (5 H, m), 7.24 (1 H, br. d, *J* = 7.3), 7.44 (1 H, br. d, *J* = 7.3), 9.44 (1 H, br. s, 10-H).

4: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.75−2.85 (2 H, m), 3.14−3.35 (2 H, m), 3.63 (3 H, s, 1-OMe), 3.81 (3 H, s, 2-OMe), 3.99 (1 H, dd, *J* = 6.7 and 7.6, 1-H), 4.81 (1 H, br. d, *J* = 7.6, 10b-H), 4.90 (1 H, d, *J* = 6.7, 2-H), 6.94−7.11 (2 H, m), 7.29 (1 H, br. d, *J* = 7.3), 7.42 (1 H, br. d, *J* = 8.1), 9.36 (1 H, br. s, 10-H).

4′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.69−2.94 (2 H, m), 3.13−3.26 (2 H, m), 3.31 (3 H, s, 1-OMe), 3.74 (3 H, s, 2-OMe), 4.01 (1 H, dd, *J* = 6.4 and 9.5, 1-H), 4.98 (1 H, br. d, *J* = 9.2, 10b-H), 5.21 (1 H, d, *J* = 6.4, 2-H), 6.93−7.10 (2 H, m), 7.25 (1 H, br. d, *J* = 8.2), 7.43 (1 H, br. d, *J* = 7.3), 9.40 (1 H, br. s, 10-H).

5: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.79−2.87 (2 H, m), 3.17 (1 H, ddd, *J* = 6.4, 6.4, and 10.7), 3.32 (1 H, ddd, *J* = 4.9, 4.9, and 10.7), 3.69 (3 H, s, 1-OMe), 3.71 (3 H, s, 2-OMe), 3.84 (1 H, dd, *J* = 8.5 and 9.5, 1-H), 4.93 (1 H, br. d, *J* = 8.5, 10b-H), 5.03 (1 H, d, *J* = 9.5, 2-H), 6.97 (1 H, ddd, *J* = 1.2, 7.0, and 7.3), 7.06 (1 H, ddd, *J* = 1.2, 7.0, and 7.3), 7.27 (1 H, br. d, *J* = 7.3), 7.40 (1 H, br. d, *J* = 7.3), 9.30 (1 H, br. s, 10-H).

6: ^{1}H NMR ([D_8]1,4-dioxane): δ = 1.47 (3 H, s, 2-Me), 2.38−2.48 (1 H, m, 1-H), 2.64−2.81 (2 H, m), 2.94 (1 H, dd, *J* = 7.3 and 12.2, 1-H), 3.12−3.36 (2 H, m), 3.43 (3 H, s, 2-OMe), 4.60 (1 H, br. dd, *J* = 6.4 and 7.3, 10b-H), 6.92−7.03 (2 H, m), 7.21 (1 H, br. d, *J* = 7.6), 7.40 (1 H, br. d, *J* = 7.0), 9.38 (1 H, br. s, 10-H).

6′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 1.28 (3 H, s, 2-Me), 2.12 (1 H, dd, *J* = 4.9 and 12.2, 1-H), 2.60−2.68 (1 H, m), 2.82−2.95 (1 H, m), 3.08 (1 H, ddd, *J* = 4.9, 9.8, and 13.4), 3.28 (1 H, dd, *J* = 8.5 and 12.2, 1-H), 3.61 (1 H, ddd, *J* = 3.7, 4.9, and 13.4), 3.69 (3 H, s, 2-OMe), 4.60 (1 H, dd, *J* = 4.9 and 8.5, 10b-H), 6.92−7.06 (2 H, m), 7.21 (1 H, br. d, *J* = 8.5), 7.40 (1 H, br. d, *J* = 7.3), 9.52 (1 H, br. s, 10-H).

7′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.43−2.56 (2 H, m, 1-H), 2.72−2.99 (2 H, m), 3.21−3.33 (1 H, m), 3.41−3.51 (1 H, m), 4.74 (1 H, br. dd, *J* = 6.7, 7.0, 10b-H), 5.23 (1 H, dd, *J* = 6.1, 8.2, 2-H), 6.95−7.09 (2 H, m), 7.20−7.47 (7 H, m), 9.45 (1 H, br. s, 10-H).

8′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 0.91 (3 H, br. t, *J* = 6.8), 1.23−1.64 (6 H, m), 2.15 (1 H, ddd, *J* = 5.8, 7.9, and 11.6), 2.34−2.44 (1 H, m), 2.52−2.82 (2 H, m), 3.08−3.31 (2 H, m), 4.25 (1 H, br. quint, 2-H), 4.49 (1 H, br. dd, *J* = 7.0 and 7.3, 10b-H), 6.96 (1 H, ddd, *J* = 1.5, 7.0, and 7.0), 7.03 (1 H, ddd, *J* = 1.5, 7.0, and 7.0), 7.21 (1 H, dd, *J* = 1.5 and 7.0), 7.40 (1 H, br. d, *J* = 7.0), 9.45 (1 H, br. s, 10-H).

9′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 1.15 (3 H, t, *J* = 7.1), 2.50 (2 H, dd, *J* = 3.5 and 5.9, 1-$H_{equiv.}$), 2.63 (1 H, ddd, *J* = 4.7, 5.9, and 15.3), 2.78−2.88 (1 H, m), 3.19 (1 H, ddd, *J* = 4.7, 7.0, and 12.9), 3.33−3.47 (2 H, m), 3.74 (1 H, dq, *J* = 7.1 and 9.4), 4.63 (1 H, t, *J* = 5.9, 10b-H), 5.13 (1 H, t, *J* = 3.5, 2-H), 6.93−7.05 (2 H, m), 7.21 (1 H, br. d, *J* = 8.2), 7.40 (1 H, br. d, *J* = 7.0), 9.35 (1 H, br. s, 10-H).

10′: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.55 (1 H, ddd, *J* = 5.9, 9.4, and 12.9, 1-H), 2.70 (1 H, ddd, *J* = 5.9, 5.9, and 15.3, 5-H), 2.80−2.91 (2 H, m, 1-H and 5-H), 3.19 (1 H, ddd, *J* = 5.9, 7.0, and 12.9, 4-H), 3.41 (1 H, ddd, *J* = 4.9, 5.9, and 12.9, 4-H), 3.70 (3 H, s, 2-OMe), 4.60 (1 H, br. dd, *J* = 5.9 and 7.0, 10b-H), 4.65 (1 H, dd, *J* = 4.7 and 9.4, 2-H), 6.97 (1 H, br. dd, *J* = 7.0 and 7.0), 7.05 (1 H, br. d, *J* = 7.0 and 8.2), 7.22 (1 H, br. d, *J* = 8.2), 7.41 (1 H, br. d, *J* = 7.0), 9.26 (1 H, br. s, 10-H).

11: ^{1}H NMR ([D_8]1,4-dioxane): δ = 2.75−2.92 (2 H, m), 3.21−3.30 (2 H, m), 4.49−4.53 (2 H, m), 4.70 (1 H, br. d, *J* = 4.7, 10b-H), 5.46 (1 H, ddd, *J* = 4.7, 4.7, and 7.0, 1-H), 7.02 (1 H, br. dd, *J* = 7.0 and 8.2), 7.11 (1 H, br. dd, *J* = 7.0 and 8.2), 7.30 (1 H, br. d, *J* = 8.2), 7.44 (1 H, br. d, *J* = 8.2), 9.61 (1 H, br. s, 10-H).

11′: ^{1}H NMR ([D$_8$]1,4-dioxane): δ = 2.73−2.64 (1 H, m), 2.82 (1 H, ddd, *J* = 8.2, 8.2, and 14.1, 1-H), 2.89−2.99 (1 H, m), 3.19−3.31 (2 H, m), 3.83 (1 H, ddd, *J* = 2.4, 4.7, and 14.1, 1-H), 4.76 (1 H, br. d, *J* = 8.2, 10b-H), 5.74 (1 H, dd, *J* = 2.4 and 8.2, 2-H), 6.97−7.13 (2 H, m), 7.24 (1 H, br. d, *J* = 7.0), 7.44 (1 H, br. d, *J* = 7.0), 9.42 (1 H, br. s, 10-H).

12: ^{1}H NMR ([D$_8$]1,4-dioxane): δ = 2.80−2.87 (2 H, m), 3.06 (1 H, ddd, *J* = 6.4, 7.3, and 10.1), 3.20 (1 H, ddd, *J* = 4.6, 5.8, and 10.1), 4.11−4.23 (2 H, m, 2-H), 4.27−4.40 (1 H, m, 1-H), 5.02 (1 H, br. d, *J* = 6.7, 10b-H), 7.01 (1 H, ddd, *J* = 1.2, 7.3, and 7.3), 7.11 (1 H, ddd, *J* = 1.2, 7.3, and 7.6), 7.37 (1 H, br. d, *J* = 7.6), 7.42 (1 H, br. d, *J* = 7.3), 7.57−7.75 (3 H, m), 8.02 (2 H, ddd, *J* = 1.5, 1.5, and 6.7), 9.35 (1 H, br. s, 10-H)

13: ^{1}H NMR ([D$_8$]1,4-dioxane): δ = 2.54−2.59 (2 H, m), 3.04−3.08 (2 H, m), 3.54−3.55 (1 H, m), 4.12 (1 H, dd, *J* = 6.7 and 8.2, 2-H), 4.37 (1 H, dd, *J* = 8.2 and 9.2, 2-H), 4.81 (1 H, br. d, *J* = 6.1, 10-H), 7.00 (1 H, ddd, *J* = 1.0, 7.3, and 7.6), 7.10 (1 H, ddd, *J* = 1.5, 7.3, and 7.6), 7.28 (1 H, br. d, *J* = 7.6), 7.42 (1 H, br. d, *J* = 7.6), 9.75 (1 H, br. s, 10-H).

13′: ^{1}H NMR ([D$_8$]1,4-dioxane): δ = 4.70 (1 H, br. d, *J* = 7.6, 10b-H), 4.92 (1 H, dd, *J* = 3.7 and 8.9, 2-H), 9.34 (1 H, br. s, 10-H), (not complete spectrum).

[1] P. N. Confalone, E. M. Huie, *Org. React.* **1988**, *36*, 1; D. St. C. Black, R. F. Crozier, V. C. Davis, *Synthesis* **1975**, 205; J. J. Tufariello, *1,3-Dipolar Cycloaddition Chemistry*, Wiley, New York, **1984**, p. 83; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Perpagamon, Oxford, **1990**, p. 269; R. Huisgen, *J. Org. Chem*. **1976**, *41*, 403.

[2] R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett, W. J. Warnock, *Tetrahedron* **1991**, *47*, 4007; R. Grigg, F. Heaney, S. Surendrakumar, W. J. Warnock, *Tetrahedron* **1991**, *47*, 4477; P. Armstrong, R. Grigg, F. Heaney, S. Surendrakumar, W. J. Warnock, *Tetrahedron* **1991**, *47*, 4495; R. Grigg, M. J. Dorrity, F. Heaney, J. F. Malone, S. Rajviroongit, V. Sridharan, S. Surendrakumar, *Tetrahedron* **1991**, *47*, 8297; R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar, W. J. Warnock, *Tetrahedron* **1992**, *48*, 6929; R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett, W. J. Warnock, *Tetrahedron* **1992**, *48*, 10399.

[3] P. De Shong, J. M. Leginus, S. W. Lander, *J. Org. Chem.* **1986**, *51*, 574; T. Kametani, S.-D. Chu, T. Honda, *J. Chem. Soc., Perkin Trans. 1* **1988**, 1598; R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Tetrahedron* **1987**, *43*, 4051; S. Masamune, W. Choy, J. S. Peterson, L. R. Sita, *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1; *Angew. Chem.* **1985**, *97*, 1−31.

[4] J. J. Tufariello, *Acc. Chem. Res.* **1979**, *11*, 369; S. A. Ali, J. H. Khan, M. I. M. Wazeer, *Tetrahedron* **1988**, *44*, 5911; A. Hall, K. P. Meldrum, P. R. Therond, R. H. Wightman, *Synlett* **1997**, 123; A. Goti, V. Fedi, L. Nanneli, F. De Sarlo, A. Brandi, *Synlett* **1997**, 577.

[5] R. Plate, P. H. H. Hermkens, J. M. M. Smits, H. C. J. Ottenheijm, *J. Org. Chem.* **1986**, *51*, 309; R. Plate, P. H. H. Hermkens, J. M. M. Smits, R. J. F. Nivard, H. C. J. Ottenheijm, *J. Org. Chem.* **1987**, *52*, 1047; P. H. H. Hermkens, R. Plate, H. C. J. Ottenheijm, *Tetrahedron* **1988**, 44, 7.

[6] S. Moriyama, Y. Vallee, *Synthesis* **1988**, 393.

[7] N. Lounasmaa, A. Toluanene, *The Alkaloids* (Ed.: G. A. Cordell), Academic Press, New York, **1992**; A. U. Rahman, A. Basha, *Biosynthesis of Indole Alkaloids*, Clarendon, Oxford, **1983**; G. A. Coedell, *Introduction to Alkaloids: A Biogenetic Approach*, Wiley, New York, **1981**; J. P. Kuntney, *Nat. Prod. Rep.* **1990**, p. 85; G. R. Pettit, F. Hogan Pierson, C. L. Herald, *Anticancer Drugs from Animals, Plants, and Microorganisms*, Wiley, New York, **1994**.

[8] K. L. Rinehart, Jr., J. Kobayashi, G. C. Harbour, S. A. Mizsak, T. A. Scahill, *J. Am. Chem. Soc.* **1984**, *106*, 1524; J. Kobayashi, G. C. Harbour, J. Gilmore, K. L. Rinehart, Jr., *J. Am. Chem. Soc.* **1984**, *106*, 1526; K. L. Rinehart, Jr., J. Kobayashi, G. C. Harbour, J. Gilmore, M. Mascal, T. G. Holt, L. S. Shield, F. Lafargue, *J. Am. Chem. Soc.* **1987**, *109*, 3378.

[9] J. W. Blunt, R. J. Lake, M. H. G. Munro, T. Toyokuni, *Tetrahedron Lett.* **1987**, *28*, 1825; R. J. Lake, M. M. Brennan, J. W. Blunt, M. H. G. Munro, L. K. Pannell, *Tetrahedron Lett.* **1988**, *29*, 2255; R. J. Lake, J. D. McCombs, J. W. Blunt, M. H. G. Munro, W. T. Robinson, *Tetrahedron Lett.* **1988**, *29*, 4971.

[10] J. Kobayashi, H. Nakamura, Y. Ohizumi, Y. Tomotake, Y. Hirata, *Tetrahedron Lett.* **1986**, *27*, 1191; O. Murata, H. Shigemori, M. Ishibashi, K. Sugama, K. Hayashi, J. Kobayashi, *Tetrahedron Lett.* **1991**, *29*, 3539.

[11] J. Kobayashi, J. Cheng, T. Ohta, S. Nozoe, Y. Ohizumi, T. Sasaki, *J. Org. Chem.* **1990**, *55*, 3666.

[12] J. H. Maarseven, P. H. H. Hermkens, E. De Clercq, J. Balzarin, H. W. Scheeren, C. G. Kruse, *J. Med Chem.* **1992**, *35*, 3223.

[13] C. Debitus, D. Laurent, M. Pais, *J. Nat. Prod.* **1988**, *51*, 799.

[14] K. Tanaka, T. Mori, K. Mitsuhashi, *Bull. Chem. Soc. Jpn.* **1993**, *51*, 799; K. Tanaka, T. Mori, K. Mitsuhashi, *Chem. Lett.* **1989**, 1115.

[15] K. Tanaka, T. Imase, S. Iwata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2243.

[16] *cis* and *trans* refer to 1-H and 10b-H; *syn* and *anti* refer to 2-H and 10b-H (2-Me and 10b-H in the case of **11** and **11′**); *cis* and *syn* adducts result from an *endo* addition; *trans* and *anti* adducts result from an *exo* addition.

[17] The kinetic selectivity towards the 2-substituted cycloadducts **6** and **6′** was also observed for methyl acrylate,[6] and has been reported earlier for the reaction of methyl methacrylate with other cyclic nitrones: S. A. Ali, J. D. Khan, M. I. M. Wazeer, *Tetrahedron* **1988**, *44*, 5911. This regioselectivity sharply contrasts with that obtained with methyl crotonate, for which only adducts **2** and **2′**, bearing the COOMe substituent in 1-position, were isolated. We believe that the regioselective formation of 2-substituted cycloadducts with methyl acrylate and methyl methacrylate is strongly governed by steric factors. In the case of methyl crotonate, with two substituents of similar bulkiness[19] at each end of the C=C double bond, the regioselectivity should be interpreted in terms of the FMO theory.[6]

[18] A. Liguori, R. Ottana, G. Romeo, G. Sindona, N. Uceela, *Tetrahedron* **1988**, *44*, 1247; J. Sims, K. N. Houk, *J. Am. Chem. Soc.* **1973**, *95*, 5798; K. N. Houk, J. Sims, R. E. Duke, Jr., R. W. Strzier, J. K. George, *J. Am. Chem. Soc.* **1973**, *95*, 7287; K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301.

[19] F. R. Jensen, C. H. Bushwell, *Adv. Alicyclic Chem.* **1971**, *3*, 139.

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