ORGANIC
LETTERS

2000
Vol. 2, No. 25
4003−4006

Photochemical Cycloaddition Reagents for Rigidly Attaching the 1,4-Dimethoxynaphthalene Chromophore to Scaffold Alkenes

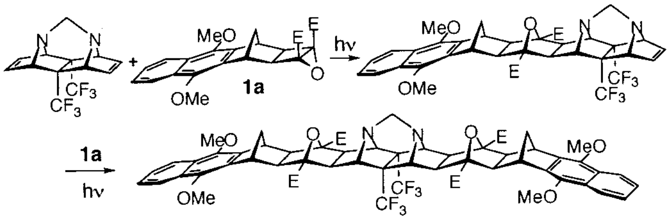
Davor Margetic,[†] Richard A. Russell,[‡] and Ronald N. Warrener*,[†]

Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland 4702, Australia, and Centre for Chiral and Molecular Technologies, Deakin University, Geelong, Victoria 3217, Australia

r.warrener@cqu.edu.au

Received September 10, 2000

ABSTRACT



The norbornanecyclobutene epoxides 1a–1c containing a fused 1,4-dimethoxynaphthalene chromophore have been reacted with cyclobutenes, cyclohexenes, norbornenes, 7-isopropylidenenorbornenes, 7-azanorbornenes, and other cyclic or electron-deficient alkenes at room temperature to form 1:1 adducts in stereoselective 1,3-dipolar cycloaddition reactions; alkynes can also participate in this reaction. The ability to form 2:1 adducts has also been demonstrated, thereby opening up opportunities for preparing functionalized products with large chromophore separations.

1,4-Dimethoxynaphthalene is a classical quencher chromophore used in the study of electron-transfer and energy-transfer reactions where geometric relationships between donor and acceptor chromophores have been shown to play an important role.[1] 1,4-Dimethoxy naphthalenes also have the potential for one-step conversion to a 1,4-naphthoquinone,[2] a related light-absorbing chromophore used in such studies.[3] We now report a versatile photochemical method for fusing the 1,4-dimethoxynaphthalene chromophore to alkenes in a geometry-predictable fashion, thereby offering an efficient route to rigid multichromophoric systems.

The thermal 1,3-dipolar cycloaddition of cyclobutene epoxides to alkenes was reported earlier by our group and now constitutes the major reaction for the stereoselective coupling of alkenes in the construction of scaffold systems.[4] The photochemical variant of that reaction, described herein, has even wider potential to deliver the versatile dimethoxynaphthalene chromophore onto alkene substrates using cyclobutene epoxide **1a**; it can be attached at room temperature, whereas the thermal reaction required heating at 140 °C. Further, **1a** can be reacted with nondipolarophilic alkenes such as cyclohexa-1,4-diene, which failed to couple under thermal conditions. The coupling is shown to display *exo,-exo*-stereoselectivity with norbornenes, yet it provides both *exo,exo* and *endo,exo* products from 7-isopropylidene norbornadienes, a feature that increases the range of stereochemical molecular architectures available to the building program. While the epoxide reagents required activating

---

[†] Central Queensland University.

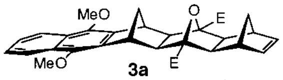
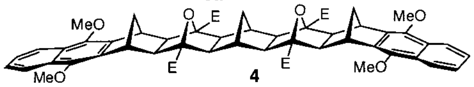
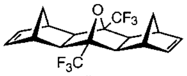
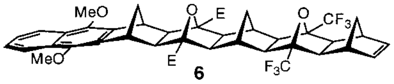
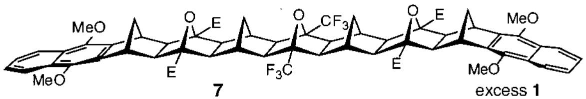
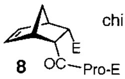
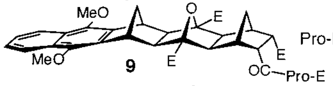
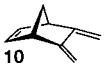
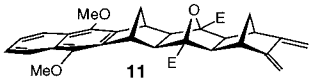
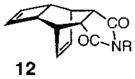
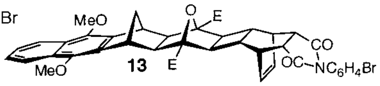
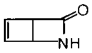
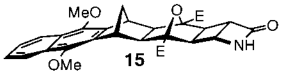
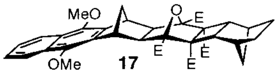
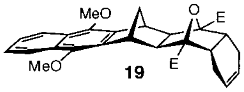
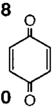
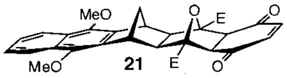
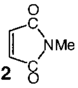
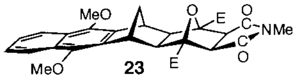
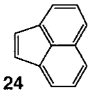
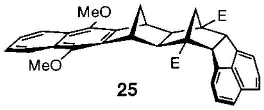
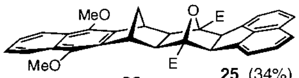
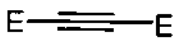
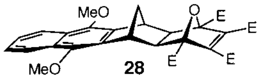
[‡] Deakin University.

(1) (a) El-Kemary, M. A.; Etaiw, S. H.; El-Baradie, H. Y. *Can. J. Anal. Sci. Spectrosc.* **1999**, *44*, 108−113. (b) Craig, D. C.; Ghiggino, K. P.; Jolliffe, K. A.; Langford, S. J.; Paddon-Row: M. N. *J. Org. Chem.* **1997**, *62*, 2381−2386. (c) El-Kemary, M. A.; El-Daly, S. A. *Monatsh. Chem.* **1996**, *127*, 593−600. (d) Ghiggino, K. P.; Clayton, A. H. A.; Lawson, J. M.; Paddon-Row, M. N. *New J. Chem.* **1996**, *20*, 853−859. (e) Kroon, Jan; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 4868−73.

(2) (a) Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* **1999**, 1474−1476. (b) Sohmiya, H.; Kimura, T.; Fujita, M.; Ando, T. *Tetrahedron* **1998**, *54*, 13737−13750.

10.1021/ol006571d CCC: $19.00

Table 1

entry	substrate	products	yields
E1 E=CO_2Me throughout	 **2**	 **3a**  **4**	87 (72%) excess **2** 43 (28%) excess 1
E2	 **5**	 **6**  **7**	excess **3** **6** 34 (8.5%) **7** (31%) excess **1** **7** (44%)
E3	 **8** chiral	 **9** Pro-E = proline ester	68 (51%)
E4	 **10**	 **11**	(66%)
E5	 **12**	R = p-C_6H_4Br  **13**	71 (65%)
E6	 **14**	 **15**	(67%)
E7	 **16**	 **17**	(72%)
E8	 **18**	 **19**	63 (37%)
E9	 **20**	 **21**	69 (57%)
E10	 **22**	 **23**	65 (27%)
E11	 **24**	 **25**  **26**	**25** (34%) **26** (43%)
E12	 **27**	 **28**	76 (45%)

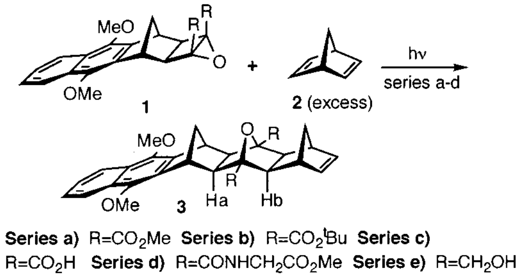
[a] Acetone, quartz, 300 nm. Reaction yields have been determined by ^{1}H NMR monitoring; isolated yields are shown in brackets and refer to recrystallized products.

groups on the 1,4-positions of the bicyclo[2.1.0]pentane component, these can be esters, acids or amides, thereby offering scope to modify the hydrophilic or lipophilic properties of the coupled product. In all cases, smooth conversion to ribbon molecules occurred by irradiation at 300 nm in acetone solution (Rayonet reactor, quartz vessel).

A selection of coupling reactions (experiments E1–E12) undergone by ester-activated cyclobutene epoxide **1a** is collected in Table 1. Reaction of **1a** with excess norbornadiene **2** (E1) gave the 1:1 adduct **3a**[5] in 87% yield; changing the ratio of reagents so that the epoxide was in excess, allowed production of the bisadduct **4** (43%) (Scheme 1). The stereochemistry of the monoadduct **3a** was assigned by NOE between protons Ha and Hb (this technique was used to establish the stereochemistry of other adducts), while the C_{2v} symmetry of the 2:1 adduct **4**, established by ^{1}H NMR, confirmed that the second addition also occurred with *exo,-exo*-stereoselectivity.

Positioning other substituents at the bridgehead positions of the coupled product allowed control of their polarity properties, and this could be achieved using the substituted epoxides **1b**–**1d**, which formed the bis(*tert*-butyl ester) **3b** (lipophilic), dicarboxylic acid **3c** (hydrophilic), and bisacyl amino acids **3d**, respectively, on reaction with excess **2**. Two electron-withdrawing substituents (esters, acids, or amides) are required for this photochemical coupling protocol to

Scheme 1



proceed, although the groups can be different. Where the groups required at the bridgehead positions are electron-donating, such as the hydrophilic hydroxymethyl groups, then this must be conducted in a secondary process after coupling, e.g., LAH reduction of the diester groups in **3a** produced the bishydroxymethyl compound **3e**.[6]

This ability to attach the 1,4-dimethoxynaphthalene chromophore to other norbornenes should have wide application since scaffold bisalkenes of various topologies are now readily available by several coupling protocols.[7] For example, irradiation of epoxide **1a** in acetone containing [3]polynorbornadiene **5**, produced in one step by reaction of norbornadiene **2** with 2,5-bis(trifluoromethyl-1,3,4-oxadiazole,[7b] furnished two coupled products, one containing one chromophore (monoadduct **6**) and the other two chromophores (the bisadduct **7**) (E2). The proportion of products **6** and **7** could be varied by modification of the molar ratio of reactants **1a** and **5**.

That reaction could be applied to chiral substrates was illustrated (E3) by fusing the 1,4-dimethoxynaphthalene chromophore *exo*-stereoselectively at the norbornene site of chiral substrate **8**[8] to form **9**; no evidence was obtained for loss of chiral integrity in this reaction.

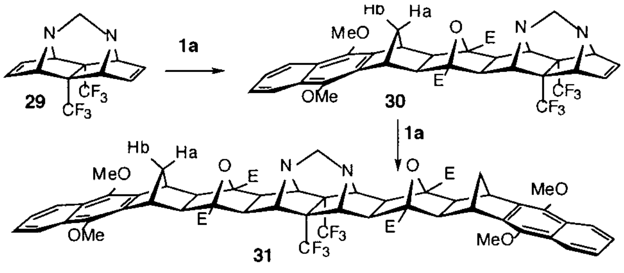
Reaction of **1a** with the bicyclic triene **10** occurred site- and stereoselectively at the norbornene π-center to afford the coupled product **11** (E4). High site selectivity was also observed in the addition to tricyclic diene **12** to form *exo*-fused cyclobutane adduct **13** (E5); the photopyridone **14** also gave an *exo*-coupled product **15** (E6). In the related reaction with the ester-substituted cyclobutene **16** (E7), the production of **17** demonstrated that the preference for *exo*-cyclobutane stereochemistry was maintained, a conclusion confirmed, in this case, by X-ray crystallography (Figure 1).

A reaction that sets this photochemical reaction apart from its thermal counterpart is the ability to add to nondipolarophilic alkenes, e.g., cyclohexa-1,4-diene **18** (E8) formed the *endo*-adduct **19** (stereochemistry confirmed by NOE). Interestingly, *exo*-coupling occurred in the related reaction of **1a** with the dienophilic *p*-benzoquinone **20** (E9) to give **21** or *N*-methyl maleimide **22** (E10) to give **23**, while acenaphthylene **24** (E11) gave almost equally the *endo*-adduct **25** and the *exo*-isomer **26**.

Smooth coupling also occurred with alkynes, e.g., irradiation of epoxide **1a** with excess dimethyl acetylenedicarboxylate **27** (E12) produced the adduct **28** in 76% yield.

Coupling of **1a** with the thermally labile bisalkene **29**[9] to give both monoadduct **30** and bisadduct **31** (Scheme 2) is a significant result since diene **29** failed to couple thermally with **1a** and also resisted coupling protocols based on reactions with 1,3-dienes, *s*-tetrazines, and 1,3,4-oxadiazoles.[7]

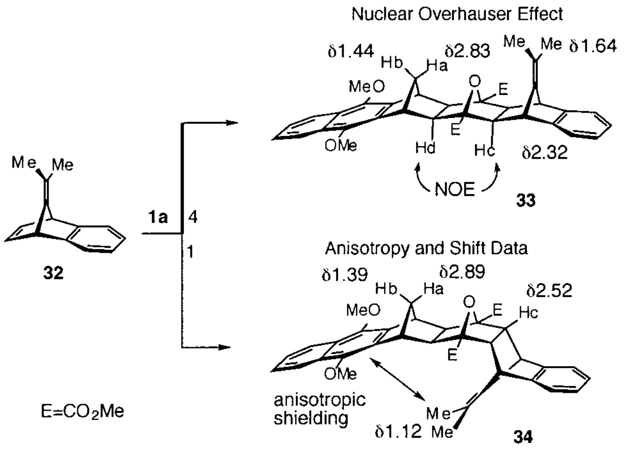
Scheme 2



The nature of the 7-substituent was important in defining the stereoselectivity of the coupling process, since reaction of **1a** with 7-isopropylidene-benzonorbornadiene **32** yielded a stereoisomeric mixture (ratio 4:1) of *exo,exo*-adduct **33** and *endo,exo*-stereoisomer **34** (Scheme 3). 7-Oxabenzonorbornadiene reacted similarly, whereas 7-azabenzonorbornadienes followed the norbornadiene model. The stereochemistry of **33** was determined by spectroscopy which showed a significant NOE enhancement between Hc and Hd; as well, the downfield chemical shift of the methano-bridge proton adjacent to the oxa-bridge was also diagnostic. The structure of its isomer **34** was supported by a similar downfield shift of one of the methano-bridge protons and the upfield shift of the isopropylidene methyl groups by the through space

Figure 1. X-ray structure of adduct **17** (stereoview).

Scheme 3



shielding provided by the benzene ring. Chemical shift data are annotated to the structures in Scheme 3.

The application of this photochemical method has been reported[4e] for the preparation of a single U-shaped cavity system, but this reaction is general and we have used it to prepare various other cavity systems from the appropriate U-shaped bisalkene.

Acknowledgment. This work was supported by the Australian Research Council and the Central Queensland University Merit Grant Scheme. We thank Dr Alan Lough, University of Toronto for conducting the X-ray structure for **17**.

OL006571D

---

(3) (a) Chen, R.; Pignatello, J. J. *J. Adv. Oxid. Technol*. **1999**, *4*, 447−453. (b) Butler, D. N.; Smits, R.; Evans, D. A. C.; Weerasuria, K. D. V.; Warrener, R. N. *Tetrahedron Lett.* **1996**, *37*, 2157−2160.

(4) (a) Butler, D. N.; Hammond, M. L. A.; Johnston, M. J.; Sun, G.; Malpass, J. R.; Fawcett, J.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 721−724. (b) Malpass, J. R.; Butler, D. N.; Johnston, M. J.; Hammond, M. L. A.; Warrener, R. N. *Org. Lett.* **2000**, *2*, 725−728. (c) Schultz, A. C.; Kelso, L. S.; Johnston, M. R.; Warrener, R. N.; Keene, F. R. *Inorg. Chem.* **1999**, *38*, 4906. (d) Warrener, R. N.; Schultz, A. C.; Johnston, M. J. Gunter, *J. Org. Chem.* **1999**, *64*, 4218. (e) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Butler, D. N.; Mahedevan, I. B.; Russell, R. A. *Org. Lett.* **1999**, *1*, 199−202. (f) Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 556. (g) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111−4114. (h) Warrener, R. N.; Margetic, D.; Russell, R. A. Article 014. *Electronic Conference on Heterocyclic Chemistry '98*; Rzepa, H. S., Kappe, O., Eds; Imperial College Press: London, 1998 (review). (i) Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 566 (review). (j) Butler, D. N.; Malpass, J. R.; Margetic, D.; Russell, R. A.; Sun, G.; Warrener, R. N. *Synlett* **1998**, 588. (k) Sun, G.; Butler, D. N.; Warrener, R. N.; Margetic, D.; Malpass, J. R. Article 062. *Electronic Conference on Heterocyclic Chemistry '98*; Rzepa, H. S., Kappe, O., Eds.; Imperial College Press: London, 1998; http://www.ch.ic.ac.uk/ectoc/echet98/pub/062/index.htm.

(5) All new compounds provided spectroscopic data consistent with structure, e.g., for **7**: ^{1}H NMR (CDCl$_3$) δ 1.39 (2H, d, $J = 9.0$ Hz); 1.61 (2H, d, $J = 9.0$ Hz); 1.77 (4H, s); 1.86 (4H, s); 2.07 (2H, d, $J = 11.0$ Hz); 2.30 (4H, s); 2.41 (4H, s); 2.70 (2H, d, $J = 9.0$ Hz); 3.59 (4H, s); 3.96 (24 H, s); 7.44−7. 46 (4H, m); 8.05−8.06 (4H, m); ^{13}C NMR δ 40.38; 41.89; 42.84; 52.39; 54.68; 55.26; 55.44; 60.37; 61.33; 87.54 (q, $^2J_{C,F} = 31.2$ Hz); 89.75; 122.15; 124.0 (q, $^1J_{C,F} = 252.0$ Hz); 125.53; 127.99; 134.08; 144.09; 169.21; ESMS ($M^+ + K$) 1221, ($M^+ + H$) 1183, ($M^+ + H_2O$) 1200. The melting points (°C) are provided for other new compounds: **3a**, 185−188; **4**, 331−332; **6**, 164−165; **7**, 289−291; **9**, 265−268; **11**, 291−293; **13**, 220−222; **15**, 198−199; **17**, 288−290; **19**, 214−216; **21**, 237−238; **23**, 231−232; **25,** 239−240; **26,** 230−232; **28**, 100−102; **30**, 111−113; **31**, 314−316; **33**, 140−142; **34**, 206−208.

(6) For related thermal reactions, see. Warrener, R. N.; Butler, D. N.; Margetic, D.; Pffeffer, F. M.; Russell, R. A. *Tetrahedron Lett.* **2000**, *41*, 4671−4675.

(7) (a) *s*-Tetrazine method: Warrener, R. N.; Margetic, D.; Russell, R. A. *Synlett* **1998**, 585−587. (b) 1,3,4-Oxadiazole method: Warrener, R. N.; Margetic, D.; Tiekink, E. R. T.; Russell, R. A. *Synlett* **1997**, 196−198. (c) Aziridine method: Butler, D. N.; Malpass, J. R.; Margetic, D.; Russell, R. A.; Sun, G.; Warrener, R. N. *Synlett* **1998**, 588−589.

(8) North, M.; Zagotto, G. *Synlett* **1995**, 639−640.

(9) Visnick, M.; Battiste, M. A. *J. Chem. Soc., Chem. Commun.* **1985**, 1621−1622.