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New and improved 'LEGO' BLOCK protocols for the direct synthesis of hydrophilic ribbon molecules with acid, ester or peptide functionality

Ronald N. Warrener,[a,*] Douglas N. Butler,[a,*] Davor Margetic,[a] Frederick M. Pfeffer[b] and Richard A. Russell[b,*]

[a]*Centre for Molecular Architecture, Central Queensland University, Rockhampton, Queensland 4702, Australia*
[b]*Centre for Chiral and Molecular Technologies, Deakin University, Geelong, Victoria 3217, Australia*

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Abstract

Hydrophilic ribbon molecules are produced directly from the reaction of cyclobutene epoxide BLOCKs with norbornene dipolarophiles or indirectly by chemical modification of substituents in preformed lipophilic ribbon molecules. The formation of di- and tetra-acid chloride epoxides holds the key to the formation of ester, acid and amide BLOCKs which are active in 1,3-dipolar cycloadditions with norbornene dipolarophiles, thereby delivering a wide range of substituents into the ribbon molecules and opening up combinatorial opportunities at each step. © 2000 Published by Elsevier Science Ltd.

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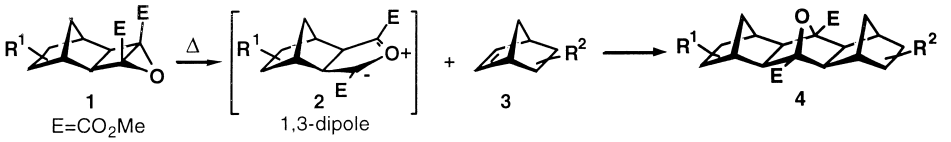
BLOCK coupling techniques based on Diels–Alder and 1,3-dipolar cycloaddition reactions have made a strong impact on the synthesis of ribbon molecules,[1] since their introduction in 1997.[2] In particular, it is now possible to couple small 'LEGO' BLOCK components[3] into rigid arrays in which the design elements of separation distance, framework topology and effector group orientation can all be addressed. Foremost in these BLOCK protocols has been the use of the ACE reaction,[2] which involves the in situ trapping of the 1,3-dipole **2**, formed by ring-opening of a cyclobutene epoxide **1**, with norbornene dipolarophiles **3** to produce rigid [*n*]polynorbornane ribbon molecules **4** capable of carrying effector groups R^1 and R^2 (Scheme 1).



Scheme 1.

* Corresponding authors.

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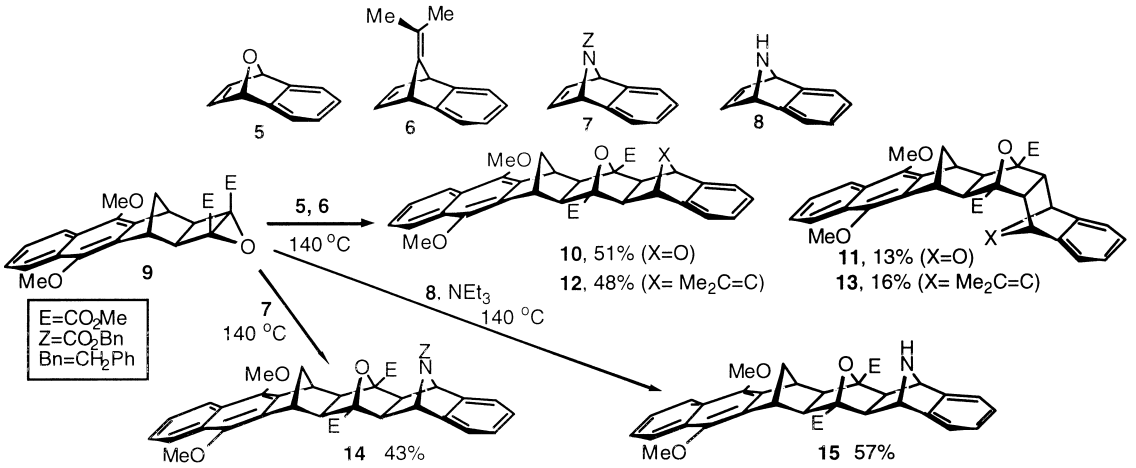
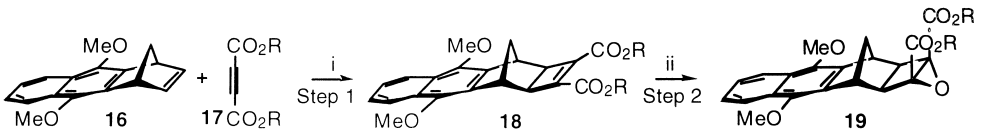
We reported in our initial disclosure[2] that a feature of the ACE reaction was the high *exo*,*exo*-stereoselectivity of the coupling step when norbornene, norbornadiene and benzonorbornadiene dipolarophiles **3** were employed. We now show that this stereoselectivity can be modulated in benzonorbornadiene dipolarophiles **5**–**8** by introducing substituents at the 7-position of the norbornadiene ring. Most change occurs by the introduction of isopropylidene or oxygen bridges, while *exo*,*exo*-stereoselectivity can be retained by using nitrogen or substituted nitrogen dipolarophiles.[1d] This control is advantageous not only in modulating the topology of ribbon molecules (Scheme 2) but also the polarity of the ribbon products, since the heteroatom bridges increase the hydrophilicity of these systems, whereas the carbon-based bridges promote lipophilicity. Thus, reaction[4] of epoxide BLOCK **9**[2] with 7-oxabenzonorbornadiene **5** gave the *exo*,*exo*-isomer **10**[5] (51%) as well as a significant proportion of the turn-frame isomer **11**[5] (13%). In a similar fashion,[4] the 7-isopropylidene-benzonorbornadiene **6** gave the extended-frame stereoisomer **12** (48%) together with the turn-frame product **13** (16%). In contrast, the *N*-benzyloxycarbonyl-7-aza-benzonorbornadiene **7**[2] reacted[4] stereoselectively with **9** to produce only the extended-frame adduct **14**. The parent 7-azabenzonorbornadiene **8** can be used to access the NH-bridged compound **15** by reaction with **9**; however, the inclusion of triethylamine is advised to stop ring-opening of **8** to naphthylamine by-products.



Scheme 2.

Our philosophy in developing the 'LEGO' BLOCK coupling protocol has been to achieve the synthesis of target molecules, replete with effector groups, directly at the assembly step, rather than conduct modifications on the ribbon molecule post coupling. To this end, we have shown that a wide range of effector groups can be introduced in this way, with some being provided by the alkene BLOCK and others by the epoxide BLOCK.[1a–f] In this respect, we were aware that the coupling process always introduced methyl ester groups at the bridgehead and that such groups had chemical potential for modification, but that would require post coupling modification in contravention of our philosophy. Consequently, we turned our attention to modification of the ester substituents in the BLOCK reagents themselves. The first indication of success came with the observation (Scheme 3) that cyclobutene-1,2-bis(*tert*-butyl) ester **18d**[5] (produced[6] by Ru-catalysed addition[7] of di(*tert*-butyl)acetylene dicarboxylate **17d** to naphthonorbornadiene **16**) could be

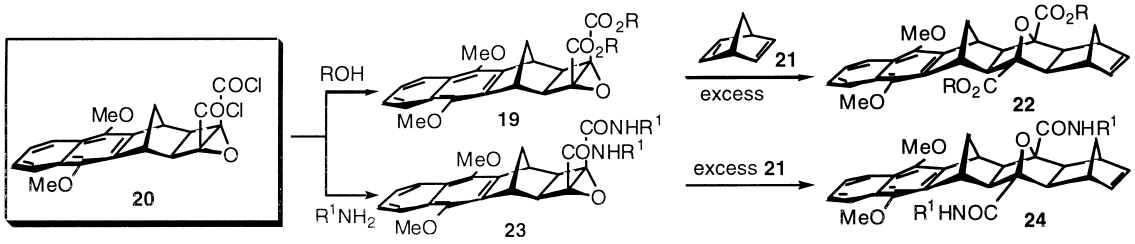
converted to the epoxide BLOCK **19d** (*tert*-BuO_2H, *tert*-BuO^-) and that ACE coupling with norbornadiene gave the corresponding ribbon molecule **22d** (Scheme 4). We now prefer, however, to prepare derivatives of **18** by ester exchange on the methyl ester **18a** (ROH, H_2SO_4), in cases where the esters are acid stable.



i) $RuH_2CO(PPh_3)_3$, *tert*-$BuO_2C{=}{=}CO_2$*tert*-Bu , C_6H_6 at reflux ii) *tert*-BuOK, *tert*-BuO_2H, RT

Series a) R=Me **Series b)** R=Et **Series c)** R=*n*-Bu **Series d)** R=*tert*-Bu **Series e)** R=H

Scheme 3.



Series a) R=Me **Series b)** R=Et **Series c)** R=*n*-Bu **Series d)** R=*t*-Bu **Series e)** R=H **Series f)** $R^1=CH_2CO_2Et$

Scheme 4.

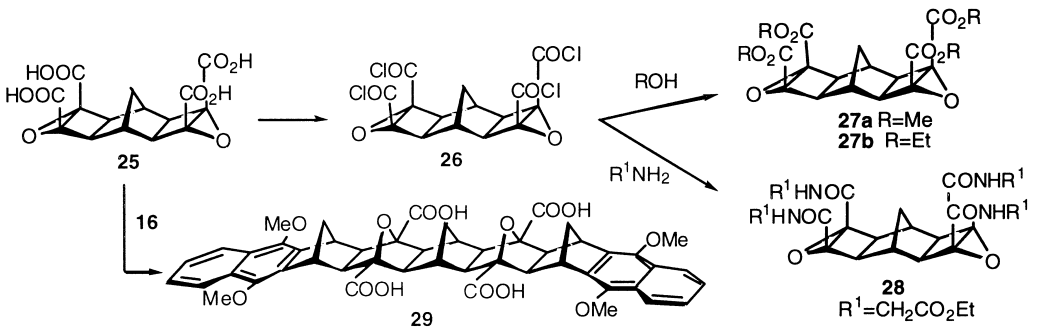
The next advance came through our ability to remove the *tert*-butyl groups from the epoxide **19d** to generate the epoxydiacid **19e** and to establish that ACE coupling with norbornadiene **21** gave the ribbon molecule **22e**. As this and related ribbon molecules derived from **19e** contain carboxylic acid groups at the bridgehead, so their hydrophilicity is improved, especially at high pH. For the first time, we were in a position to produce ribbon molecules with substituents at the bridgehead other than methyl esters. The quantum breakthrough came with the realisation that ester-substituted cyclobutene epoxides were far more robust than their simple epoxide counterparts and would tolerate both acidic (as above) and basic conditions.[8] The stability of the epoxide to base was forcefully illustrated by the saponification of the methyl ester groups of **19a** to the corresponding dicarboxylic acid **19e** in 90% yield by refluxing overnight in aq. KOH in methanol/THF. Conversion of diacid **19e** to the diacid chloride **20** by treatment with oxalyl chloride or thionyl chloride provided a wonderful springboard to epoxyester BLOCKs **19a–d** or epoxyamide BLOCKs **23**[9] by reaction with alcohols or primary or secondary amines, respectively. Further, the amide BLOCKs **23** derived from primary amines, or amino acid esters reacted with norbornadiene to afford the amide-substituted ribbon molecules **24**. Thus, the opportunity to control lipophilic properties using peptide side chains is also now a viable option. The range of simple alcohol or amine displacement reactions which can be used in the conversion of the acid chloride **20** to derivatives **19** or **23**, together with the variety of norbornene dipolarophiles that can participate in the coupling protocol, has opened the way for the preparation of combinatorial libraries of ribbon molecules.

The use of this methodology for complex ribbon molecule synthesis is strengthened by some preliminary results on the known dual cyclobutene epoxide BLOCK **27a**.[2] Hydrolysis to the tetracid

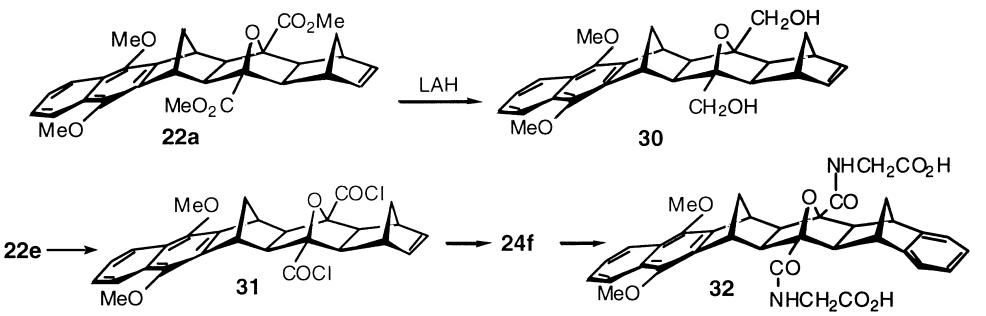
25, conversion to the tetra(acid chloride) **26** and transformation to the tetra-ester **27b** or the tetra-amide **28** was achieved in an analogous fashion to that used for the corresponding reactions on **20** discussed above. The application of these dual epoxides **26**–**28** to ribbon molecule synthesis is typified by the reaction of tetra-acid bis-epoxide **25** with naphthonorbornadiene **16** to form the [5]polynorbornane tetracarboxylic acid **29**.

Conversion of the cyclobutene-1,2-diesters **18** to their epoxides **19** (Scheme 3) required a nucleophilic epoxidising agent, a transformation previously conducted using *tert*-butyl hydroperoxide and 1 equivalent of methyllithium at –78°C.[2] It has now been found that this step can be achieved in better yields and without the complications associated with by-product formation using *tert*-butyl hydroperoxide and potassium *tert*-butoxide as the base. Under these new conditions, the reaction can be conducted at room temperature using catalytic amounts (10 mol%) of potassium *tert*-butoxide and yields >80% are achieved.

Finally, the need for electronic stabilisation of the intermediate 1,3-dipolar intermediate **2** means that not all substituents can be delivered via the ACE assembly protocol. Accordingly, we report briefly on ester group modification in the ribbon molecules, appreciating that such transformations are subject to the chemical tolerance of the effector groups present in the system. Reduction (LAH in THF) of the two ester groups in **22a** (or related diester derivatives) produced the bis-hydroxymethyl system **30**[5] thereby increasing the hydrophilicity of the ribbon molecule (Scheme 5). Other transformations include hydrolysis of the ester groups in **22a** to the dicarboxylic acid **22e**, formation of the di(acid chloride) **31** with oxalyl chloride, and its conversion to glycine ester amide **24f** by reaction with ethyl glycinate and selective ester hydrolysis of **24f** in base to form the *N*-acylated glycine **32** (Scheme 6). The latter compound **32** is suitable for the introduction of



Scheme 5.



Scheme 6.

peptide linkages at the original ester bridgehead positions of the ribbon molecule and such transformations, and their potential application to peptide and protein chemistry, are currently being explored in our laboratories.

Acknowledgements

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References

1. (a) Schultz, A. C.; Kelso, L. S.; Johnston, M. R.; Warrener, R. N.; Keene, F. R. *Inorg. Chem.* **1999**, *38*, 4906–4909. (b) Warrener, R. N.; Schultz, A. C.; Johnston, M. R.; Gunter, M. J. *J. Org. Chem.* **1999**, *64*, 4218–4219. (c) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Russell, R. A. *Org. Lett.* **1999**, *1,* 203–206. (d) Warrener, R. N.; Margetic, D.; Russell, R. A. *Synlett* **1998**, 585–587. (e) Warrener, R. N.; Margetic, D.; Amarasekara, A. S.; Foley, P.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1999**, *40*, 4111–4114. (f) 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, 1998 (review). (g) Warrener, R. N.; Butler, D. N.; Russell, R. A. *Synlett* **1998**, 566–573 (review). (h) Butler, D. N.; Malpass, J. R.; Margetic, D.; Russell, R. A.; Sun, G.; Warrener, R. N. *Synlett* **1998**, 588–589. (i) 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, 1998 (http://www.ch.ic.ac.uk/ectoc/echet98/pub/062/index.htm). (j) 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. (k) Malpass, J. R.; Butler, D. N.; Johnston, M. J.; Hammond, M. L. A.; Warrener, R. N. *Org. Lett.* **2000**, *2,* 725–728.
2. Warrener, R. N.; Schultz, A. C.; Butler, D. N.; Wang, S.; Mahadevan, I. B.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1997**, 1023–1024.
3. For alternative types of 'LEGO' building block techniques, see: (a) Ashton, P. R.; Girreser, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Raymo, F. M.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1993**, 5422–5429. (b) Pabst, G. R.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8817–8820.
4. These reactions could also be conducted under photochemical conditions (rt, benzene, 360 nm). Warrener, R. N.; Margetic, D.; Russell, R. A. 1999, unpublished.
5. All new compounds were characterised by spectroscopic data and high resolution ms. Mp (°C) and yields of a selection of new products are as follows: **10**: 156–158, 51%; **11**: 180–182, 13%; **14**: 156–158, 43%; **18c**: oil, 95%; **18d**: oil, 35%; **19b**: 200–202, 89%; **19c**: 99–101, 50%; **19d**: 177–180, 58%; **20**: 223–225, 80%; **23f**: oil, 76%; **24f**: 112–114, 48%; **27b**: oil, 67%; **28**: >300, 80%; **29**: >300, 66%; **31**: 107–108, 84%, **32**: >350, 81%.
6. This reaction was noteworthy since it showed that even bulky *tert*-butyl groups could be tolerated in the [2+2] cycloaddition process, a reaction hitherto restricted to the methyl esters of acetylene dicarboxylates.[7] In a practical sense, however, we have found that it is more effective to conduct ester exchange on the cyclobutene-1,2-dimethyl ester **18a**, thereby avoiding preparation of the different acetylenic diesters **17**. This exchange is typified by the conversion of dimethyl ester **18a** to the di(*n*-butyl) ester **18c** by reaction with *n*-butanol containing H_2SO_4.
7. (a) Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492–4496. (b) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580–581. (c) Warrener, R. N.; Pitt, I. G.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1983**, 1340–1342. (d) Kumar, K.; Tepper, R. J.; Zeng, Y.; Zimmt, M. B. *J. Org. Chem.* **1995**, *60*, 4051–4066.
8. The stability of the epoxide rings in these compounds was surprising; we attribute this to the reluctance of the epoxide ring to open under acidic conditions owing to the poor stabilisation of the incipient carbocation; base stability is attributed to the inability of nucleophiles to attack from the backside of the epoxide for steric reasons.
9. We find that epoxyamides like **23** cannot be formed by epoxidation of the corresponding cyclobutene-1,2-dicarboxamides; even tertiary amides fail. The epoxidation reaction also fails when the ester substituents are replaced with two CF_3, one CF_3 and one CO_2Me or two SO_2Ph groups (we thank Professor O. DeLucchi for providing this latter sample).