CSIRO PUBLISHING

Rapid Communication

www.publish.csiro.au/journals/ajc

Aust. J. Chem. **2003**, *56*, 263–267

Position-Addressable Nano-Scaffolds. I. The Preparation of *N,O*-, *N,C*- and *N,N*-Bridged Sesquinorbornadiene Succinimides as Compact, Highly Functionalized Addressable Building Blocks

Ronald N. Warrener,[A,C] *Davor Margetic*,[A] *Guangxing Sun*[A] *and Richard A. Russell*[B]

[A] Centre for Molecular Architecture, Central Queensland University, Rockhampton 4702, Australia.
[B] Centre for Chiral and Molecular Technologies, Deakin University, Geelong 3217, Australia.
[C] Author to whom correspondence should be addressed (e-mail: r.warrener@cqu.edu.au).

Succinimide-functionalized *N,O*-, *N,C*-, and *N,N*-bridged benzo[2]polynorbornanes (benzosesquinorbornadienes) are reported for the first time and are prepared by the cycloaddition of either five-membered cyclic 1,3-dienes onto *N*-substituted benzo-7-azanorbornadienomaleimides or *N*-substituted isoindoles onto the appropriate norbornadienomaleimides. These products contain an end-fused norbornene (or a 7-substituted relative) and have been designed to act as alkene BLOCKs for the production of nano-scaffolds with up to six addressable sites supplied by each norbornene unit. The *N*-bridges in these BLOCKs (and their coupled products) allow *N*-substituent mobility by invertomerization of the sp^3 nitrogen whereas the *N*-substituents on the succinimides are attached to an sp^2 nitrogen atom and remain static. Preferred invertomer geometry can be determined using molecular modelling.

Manuscript received: 21 October 2002.
Final version: 9 December 2002.

Introduction

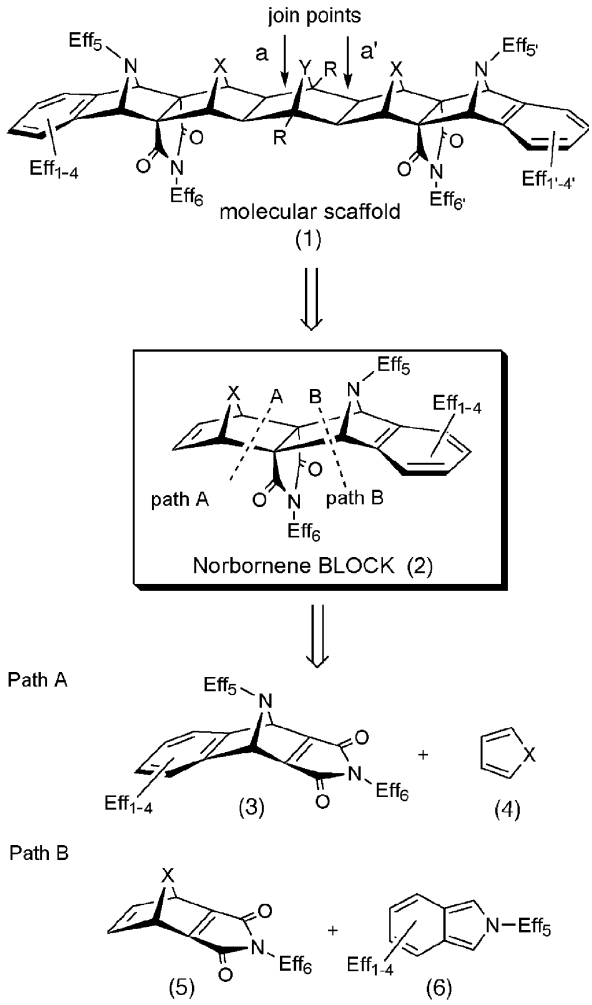
In recent years, our group has developed 'LEGO'-like building block techniques for the construction of carbocyclic scaffolds which allow the attachment of functional units ('effector groups', for definition see ref. [1]) to specific positions of a carbocyclic frame.[2,3] This protocol is based on cycloaddition strategies involving the fusion of norbornenes together (stepwise or in concert) or their linking to a central spacer component and has been used by us[4–6] and others[7,8] to produce rigid molecular scaffolds containing a variety of chromophore combinations and frame geometries. Functionalized scaffolds of this type have been applied to supramolecular assemblies and as dyads for the elucidation of energy and electron transfer mechanisms.[6,8] When scaffold construction involves a separate central spacer unit, fusion with norbornene reagents (BLOCKs) produce molecular scaffolds which attain nanometre dimensions (nano-scafffolds). Size alone is unimportant unless the nano-scaffold can bear functionality at specific locations. Such addressable nano-scaffolds encompass the smaller systems reported by Mutter and coworkers[9,10] for use in peptide chemistry (RAFTs) in which carbocyclic templates were used to hold peptide functionality.

The [*n*]polynorbornane nano-scaffolds (1) are elegantly suited for locating different types of effector functionality onto the molecular framework and are readily assembled from norbornene BLOCKs (2) (Scheme 1).[1] Each BLOCK can carry its own effector functionality, introduced sequentially during the course of its synthesis, and such functionality is position-specifically transported to the molecular scaffold in the course of the BLOCK assembly process. The resultant nano-scaffold, e.g. (1), has not only the individual effectors provided by the BLOCKs but also X groups (O, NR, C=N, N=N) and R groups (CO_2H, CO_2R, CF_3, pyridyl etc.) introduced during the various assembly protocols. By working in the field of *N*-bridged bicyclo[2.2.1]heptene chemistry, the method offers an unprecedented opportunity for introducing dynamic linkages by the attachment of effectors as *N*-bridged substituents. The present study reports the first syntheses of compact, addressable, *N*-bridged building BLOCKs (2) (Scheme 1) suitable for the construction of nano-scaffolds of type (1).

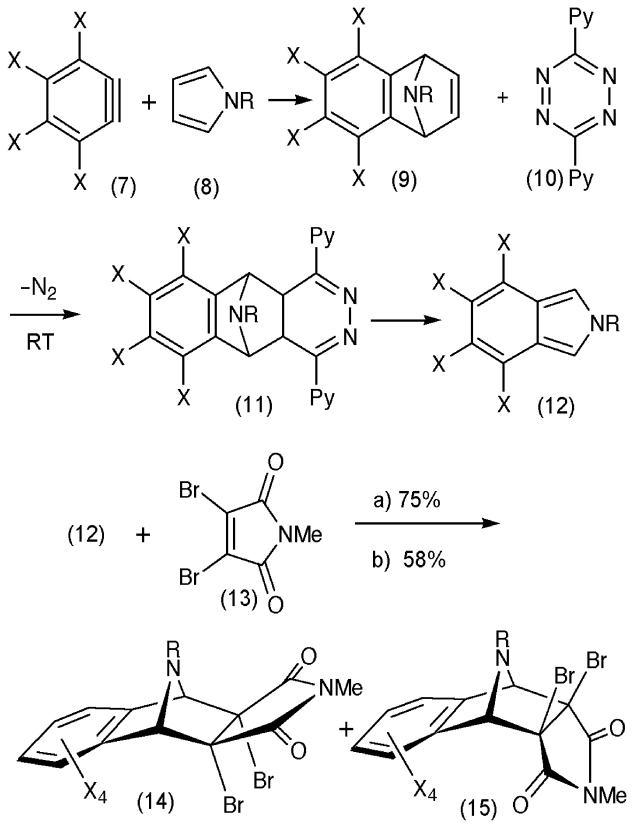
Results and Discussion

The benzo-*N*,X-[2]polynorbornadienes (2) where X = C, N, and O have been identified as the centrepiece of the synthetic strategy. The *N,C*-bridged systems have a norbornene subunit at the terminus of the BLOCK for which stereoselective coupling usually affords coupled products with the extended-frame geometry as depicted in (1). Modification of the 7-position of the norbornene (X = O, NR′) can be used to access isomers of (1) at the BLOCK coupling step.[3,11] Furthermore, there are good opportunities for the synthesis of stereochemical variants of the BLOCKs (2) using paths A and B outlined in Scheme 1.[12]

 10.1071/CH02218 0004-9425/03/04263



Scheme 1. In (1), the Y-bridge and R groups are introduced during the coupling process. Eff_1–Eff_6 are various effector groups.



Scheme 2. Series A: X = H, R = CO_2Bn. Series B: X = F, R = Bn.

In the path A approach, all the addressable sites are associated with the highly dienophilic benzo-7-azanorbornadienomaleimide (3), the synthesis of which has not previously been reported. By contrast, the path B approach distributes the effector linkage-points between the known reagents, 7-oxanorbornadienomaleimide (5, X = O),[13] and the *N*-substituted isoindoles (6).[14–16]

We have used a convergent approach for the construction of the desired benzo-7-azanorbornadienomaleimides (16) and (17) in which up to six effector sites (Eff_1–Eff_6) have been identified and introduced site-selectively by prior attachment to the different precursor reagents. This method started from the addition of benzynes (7) (carrying up to four effectors X) to *N*-substituted pyrroles (carrying R = Eff_5 as the *N*-substituent) to form 7-azabenzonorbornadienes (9) in which five of the effector groups were selectively positioned (Scheme 2). The remaining effector group (Eff_6) was introduced by way of the *N*-substituent of 3,4-dibromomaleimide (13) (in this case a methyl group, derived by alkylation of 3,4-dibromomaleimide with methyl iodide). Eff_6 finally appears as the *N*-substituent of the succinimide ring in BLOCKs (23)–(32) (Table 1), following cycloaddition of the various cyclic 1,3-dienes to the key benzonorbornadienomaleimide intermediates (16) and (17) (Scheme 3).

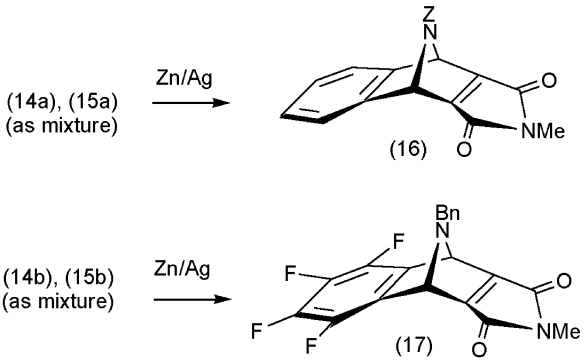
The method used for the formation of the dibromomaleimide adducts (14a)/(15a) and (14b)/(15b) depended on the stability of the *N*-substituted isoindole. For the more reactive *N*-CO_2Bn isoindole (12a), adduct formation [(14a) : (15a) = 3 : 1] could be achieved by generation of (12a) in situ in the presence of *N*-methyl 3,4-dibromomaleimide (13) (the *N*-methyl group is used as the prototype substituent for Eff_6) at room temperature using our s-tetrazine route from *N*-CO_2Bn 7-azabenzonorbornadiene (Scheme 1).[12] In the case of the less reactive, but isolable, *N*-benzyl 4,5,6,7-tetrafluoroisoindole (12b), forcing conditions at high pressure (14 kbar, RT, 1 week) were required to effect adduct formation [(14b) : (15b) = 10 : 1] between the *N*-methyl 3,4-dibromomaleimide (13) and isoindole (12b). The proton chemical shifts of the *N*-Me resonances were used to assign stereochemistry to the adducts since, in the minor *endo*-imide adducts (15a) and (15b), the methyl groups were shielded by the aromatic ring and resonated at higher field than those in the *exo*-imide isomers (14a) and (14b), respectively (see Table 2). Significantly, the major isomers (14a) and (14b) possessed *endo*-bromine substituents, a helpful stereochemical feature for effective debromination.*

* The adduct of DBM (1) with cyclopentadiene has the bromine substituents in the *exo*-position and formed a product derived from trapping of an intermediate radical by the furan co-reagent.

Table 1. Product formation from the addition of a selection of cyclic 1,3-dienes (18)–(22) to azanorbornadieno-maleimides (16) or (17)

Entry	Reaction	X, Y	Adduct (*syn*)	Relative percentage	*N*-Me	Adduct (*anti*)	Relative percentage	*N*-Me	Yield(%)[A]
1	(16) + (18)	H, C	(23)	33	δ 2.12	(28)	67	δ 2.26	23
2	(16) + (19)	H, O	(24)	–	–	(29)	100	δ 2.32	49
3	(16) + (20)	H, C=C	(25)	33	δ 2.16	(30)	67	δ 2.20	20
4	(16) + (21)	H, NZ	(26)	100	δ 2.10	(31)	–	–	28
5	(17) + (22)	F, NAc	(27)	100	δ 2.39[B]	(32)	–	–	not detected

[A] Yields are for isolated and recrystallized products. Reactions conducted on < 0.5 mmol scale: yields not optimized.
[B] Shifted downfield 0.25 ppm by fluorine groups, see (15a) versus (15b).

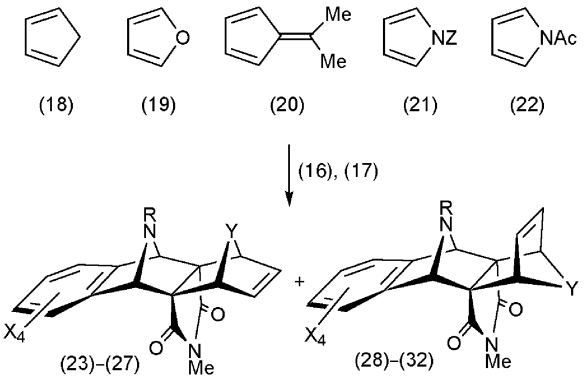


Scheme 3. (16) and (17) are formed in situ and trapped with 1,3-dienes. $Z = CO_2Bn$.

Table 2. Proton chemical shifts δ of the N-methyl groups in adducts (14) and (15)

Isoindole	Adducts	*N*-Me	Adducts	*N*-Me	Ratio
(12a)	(14a)	3.20	(15a)	2.63	3 : 1[A]
(12b)	(14b)	3.09	(15b)	2.39	10 : 1[B]

[A] Conditions: relux, toluene, 90°C, 2 h; isolated yield.
[B] Conditions 14 kbar, room temp., dichloromethane, 1 week; spectroscopic yield.



Scheme 4. $Z = CO_2Bn$

Formation of the previously unknown benzo-7-azanor-bornadienomaleimides (16) and (17) was achieved by oxidative debromination (Zn/Ag couple) of the respective dibromo-adducts (14a, 15a) and (14b, 15b) (Scheme 4). Such compounds were too unstable for isolation and were generated in situ in the presence of the trapping cycloaddition agent. Complete stereoselectivity occurred in the reactions of dienophile (16) with furan (19) (Table 1, Entry 2) to form the *anti*-bridged adduct (29) and with *N*-CO_2Bn-pyrrole (21) (Entry 4) to afford the *syn*-bridged product (26), thereby opening up ways to access adducts of either frame geometry.

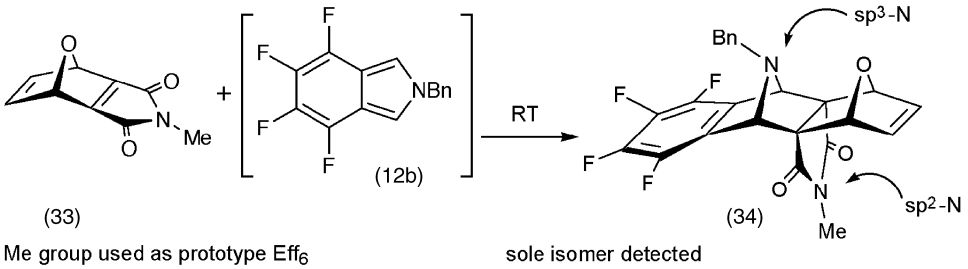
For cases in which both adduct geometries were required, these could be achieved by reaction with cyclopentadiene (18) (favoring *anti*-isomer (28) 2 : 1) (Table 1, Entry 1) or 6,6-dimethylfulvene (favouring *anti*-isomer (30) 2 : 1) (Table 1, Entry 3). The reaction of *N*-acetylpyrrole (22) with the tetrafluorinated dienophile (17) (prototype for effectors 1–4) gave exclusively the *syn*-adduct (27) (Table 1, Entry 5). Again, the upfield shift of the succinimide *N*-Me proton resonances in adducts with *endo*-succinimide geometry were used to assign adduct stereochemistry (see Table 1)

The path B cycloaddition of *N*-benzyl 5,6,7,8-tetrafluoro-isoindole (12b) (the benzyl group served as the model substituent for Eff_5) with *N*-methyl-7-oxanorbornadieno-maleimide (33) formed a single stereoisomer (21%) which was shown to have the *syn-N,O*-bridged structure (34) (Scheme 5).[†] This result highlighted the ability of the path A and B combinations to achieve new *and different* structural outcomes as the *anti-N,O*-bridged system (29) was formed exclusively in the reaction of (16) with (19).

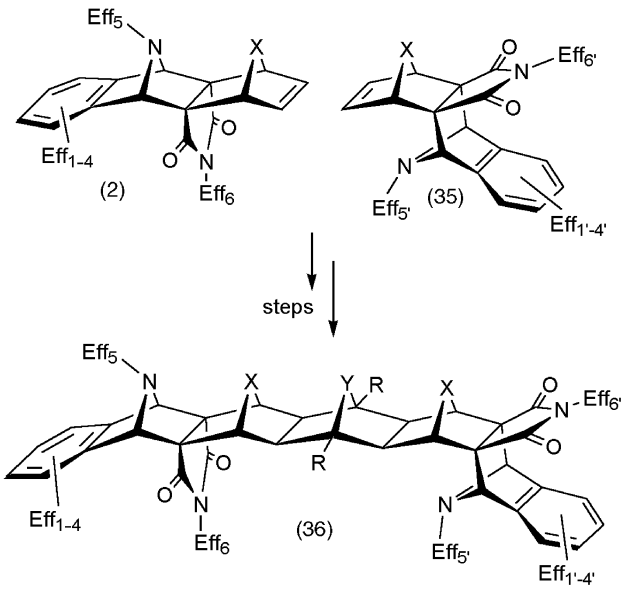
A special feature of all these building BLOCKs is the presence of at least one *N*-bridge. Substituents (Eff_5) attached to such *N*-bridges (sp^3 hybridized N) have been shown to undergo invertomerization in related systems. Accordingly, such effectors have novel dynamic properties and stand in contrast with *N*-substituents (Eff_6) attached to the succinimide rings in which the nitrogen is sp^2 hybridized and fixed in geometry. Reference to BLOCK (34) (Scheme 5) shows that the benzyl substituent is oriented over the aromatic ring and this is the preferred invertomer. This assignment is based on molecular modelling predictions, but is in keeping with other studies in which similar invertomer preferences have been supported by nuclear Overhauser effect experiments in solution and solid-state X-ray studies.[17]

In the accompanying communication,[18] we demonstrate that functionalized alkene BLOCKs, similar to the type

[†] The *N*-methyl resonanance of extended-frame adduct (34) occurred at δ 2.39 almost the same as for the bent-frame tetrafluoro adduct (29) (δ 2.32). However, the expected upfield shift owing to shielding by both the aromatic ring and the alkene, represents another case where the fluorinated aromatic ring has a modifying effect (see Table).



Scheme 5.



Scheme 6.

described herein, can form dual 1,3-dipolar coupled products of the nano-scaffold type. As the norbornene blocks can be coupled stepwise in some procedures, so this opens the way to produce different nano-scaffold geometries. For example, nano-scaffold (1) can be accessed through the coupling of two BLOCKs of type (2) whereas the coupling of (2) with its isomer (35) would produce the nano-scaffold (36) in which the two imides (and their effectors) are on opposite sides of the scaffold frame (Scheme 6).

The additional feature to note in this type of coupling is the opportunity to introduce additional effector groups at the R-positions of (1) and (36) thereby allowing edge substitution of the nano-scaffold.[19]

Conclusion

This paper has demonstrated how norbornene BLOCKs with multiple addressable sites can be prepared from *N*-substituted benzo-7-azanorbornadienenomaleimides in differing geometrical shapes (path A), e.g. exclusively extended-frame topology using addition of furan, exclusively bent-frame topology by addition of *N*-(CO_2Bn)-pyrrole, and mixtures of both with cyclopentadiene or 6, 6-dimethylfulvene. An alternative combination of reagents, e.g. 7-oxanorbornadienomaleimide with *N*-substituted isoindoles (path B), where the diene carries the benzo ring allows a complementary approach to these same products but under different stereocontrolling factors. Such adducts, containing up to six addressable effector sites (the imide ring, the *N*-bridge, and the aromatic ring) retain a norbornene or 7-substituted norbornene π-bond at the terminus which makes them suitable for use as BLOCK reagents in the preparation of functionalized molecular nano-scaffolds.

Experimental

All compounds were characterized by one-dimensional and two-dimensional nuclear magnetic resonance spectroscopy and high-resolution mass spectrometry (HRMS). Representative compounds follow.

Compound (23). mp 191–192°C; δ_H ($CDCl_3$) 1.72 (1 H, d, *J* 9.3), 2.12 (3 H, s), 3.15 (2 H, d, *J* 9.3), 3.36 (2 H, s), 5.02 (2 H, s), 5.40 (2 H, s), 6.28 (2 H, s), 7.08–7.30 (9 H, m); δ_C ($CDCl_3$) 24.07, 47.18, 49.78, 65.97, 68.16, 122.50, 123.16, 128.17, 128.80, 129.16, 136.59, 140.84, 156.03, 176.95; HRMS found 426.1572, $C_{26}H_{22}N_2O_4$ requires *m*/*z* 426.1579.

Compound (25). Not isolated; δ_H ($CDCl_3$) 1.44 (3 H, s), 1.61 (3 H, s), 2.16 (3 H, s), 3.81 (1 H, s), 3.84 (1 H, s), 4.94 (1 H, d, *J* 12.2), 5.03 (1 H, d, *J* 12.2), 5.37 (1 H, s), 5.46 (1 H, s), 6.36 (2 H, s), 7.08–7.36 (9 H, m).

Compound (28). mp 141–142°C; δ_H ($CDCl_3$) 1.46 (1 H, d, *J* 9.8), 1.68 (1 H, d, *J* 9.8), 2.26 (3 H, s), 3.31 (1 H, s), 3.35 (1 H, s), 4.91 (1 H, d, *J* 12.2), 5.16 (1 H, d, *J* 12.2), 5.22 (1 H, s), 5.25 (1 H, s), 5.96 (1 H, s), 6.26 (1 H, s), 7.08–7.34 (9 H, m); δ_C ($CDCl_3$) 24.70, 47.15, 52.11, 62.61, 62.90, 67.65, 122.43, 122.03, 127.98, 128.15, 128.76, 128.91, 129.19, 134.14, 134.91, 137.01, 144.00, 144.47, 152.17, 177.67; HRMS found 426.1576, $C_{26}H_{22}N_2O_4$ requires *m*/*z* 426.1579.

Compound (29). mp 147–148°C; δ_H ($CDCl_3$) 2.32 (3 H, s), 4.91 (1 H, d, *J* 12), 5.18–5.21 (5 H, m), 6.20 (1 H, d, *J* 5), 6.54 (1 H, d, *J* 5), 7.11–7.37 (9 H, m); δ_C ($CDCl_3$) 24.80, 60.53, 60.83, 67.66, 68.70, 81.94, 122.00, 122.39, 128.06, 128.63, 128.87, 129.03, 134.56, 134.86, 136.42, 143.43, 143.90, 152.43, 175.96; HRMS found 428.1385, $C_{25}H_{20}N_2O_5$ requires *m*/*z* 428.1372.

Compound (30). mp 116–119°C; δ_H ($CDCl_3$) 1.39 (3 H, s), 1.40 (3 H, s), 2.20 (3 H, s), 3.80 (1 H, s), 3.85 (1 H, s), 4.96 (1 H, d, *J* 12.2), 5.17 (1 H, d, *J* 12.2), 5.26 (1 H, s), 5.30 (1 H, s), 6.02 (1 H, s), 6.35 (1 H, s), 7.08–7.36 (9 H, m).

Compound (34). mp 208–209°C; δ_H ($CDCl_3$) 2.39 (3 H, s), 3.40 (2 H, s), 4.93 (2 H, s), 5.32 (2 H, s), 6.57 (2 H, s), 7.26–7.32 (5 H, m); δ_C ($CDCl_3$) 24.96, 52.96, 67.47, 68.40, 82.11, 126.37, 128.33, 128.89, 129.43, 138.06, 139.43, 146.10, 174.29; HRMS found 456.1099, $C_{24}H_{16}F_4N_2O_3$ requires *m*/*z* 456.1097.

Acknowledgments

We thank the Australian Research Council for funding this research and G. S. thanks Central Queensland University for the award of a Ph.D. scholarship.

References

[1] R. N. Warrener, D. N. Butler, R. A. Russell, *Synlett* **1998**, 387.
[2] R. N. Warrener, A. C. Schultz, D. N. Butler, S. Wang, I. B. Mahadevan, R. A. Russell, *Chem. Commun.* **1997**, 1023.
[3] R. N. Warrener, D. Margetic, P. J. Foley, D. N. Butler, A. Winling, K. A. Beales, R. A. Russell, *Tetrahedron* **2001**, *57*, 571.
[4] M. R. Johnston, M. J. Gunter, R. N. Warrener, *J. Chem. Soc., Chem. Commun.* **1998**, 2739.
[5] A. C. Schultz, L. S. Kelso, M. R. Johnston, R. N. Warrener, F. R. Keene, *Inorg. Chem.* **1999**, *38*, 4906.
[6] L. S. Kelso, T. A. Smith, A. C. Schultz, P. C. Junk, R. N. Warrener, K. P. Ghiggino, F. R. Keene, *J. Chem. Soc., Dalton Trans.* **2000**, 2599.
[7] A. Lutzen, S. D. Starnes, D. M. Rudkevich, J. Rebek, Jr, *Tetrahedron Lett.* **2000**, *41*, 3777.
[8] K. A. Jolliffe, S. J. Langford, A. M. Oliver, M. J. Shephard, M. N. Paddon-Row, *Chem. Eur. J.* **1999**, *5*, 2518.
[9] I. M. Eggleston, M. Mutter, *Chem. Britain* **1996**, 39.
[10] G. V. Nikiforovich, M. Mutter, C. Lehmann, *Biopolymers (Peptide Science)* **1999**, *50*, 361.
[11] R. N. Warrener, D. N. Butler, D. Margetic, R. A. Russell, *ECHET98 Electronic Conference on Heterocyclic Chemistry* **1998**, June 29–July 24, 73.
[12] D. N. Butler, D. Margetic, P. J. C. O'Neill, R. N. Warrener, *Synlett* **2000**, 98.
[13] R. N. Warrener, G. M. Elsey, L. Maksimovic, M. R. Johnston, C. H. L. Kennard, *Tetrahedron Lett.* **1995**, *36*, 7753.
[14] G. M. Priestley, R. N. Warrener, *Tetrahedron Lett.* **1972**, *42*, 4295.
[15] J. R. Malpass, G. Sun, J. Fawcett, R. N. Warrener, *Tetrahedron Lett.* **1998**, *39*, 3083.
[16] R. N. Warrener, *Eur. J. Org. Chem.* **2000**, 3363.
[17] R. N. Warrener, D. N. Butler, unpublished results.
[18] R. N. Warrener, H. Sun, M.R. Johnston, *Aust. J. Chem.* **2003**, *56*, 269.
[19] R. N. Warrener, D. N. Butler, D. Margetic, F. M. Pfeffer, R. A. Russell, *Tetrahedron Lett.* **2000**, *41*, 4671.