Pergamon

Tetrahedron Letters 43 (2002) 5981–5984

TETRAHEDRON
LETTERS

An efficient and novel stereoselective protocol for the construction of *syn*-facially bridged norbornane frameworks

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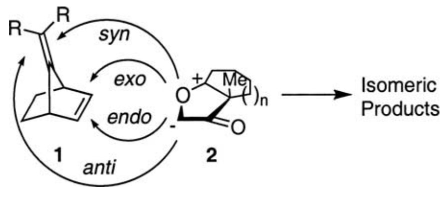
Received 12 May 2002; revised 12 June 2002; accepted 27 June 2002

Abstract—An efficient protocol for the synthesis of *syn*-facially bridged norbornane frameworks has been developed via tandem cyclization–cycloaddition reactions of rhodium carbenoids generated from α-diazo ketones. Using this new methodology, various functionalized *syn*-facially bridged norbornane frameworks have been synthesized in a stereoselective manner.

Diels–Alder or 1,3-dipolar cycloaddition reactions offer a convenient route for the stereoselective construction of complex molecular structures. Block-coupling methodologies based on Diels–Alder or 1,3-dipolar cycloaddition reactions have gained substantial attention in the synthesis of ribbon molecules.[1,2] Recently, the development of block coupling methodology using 1,3-dipolar cycloaddition for the construction of [*n*]polynorbornane scaffolds has been well documented.[2] Generally, thermal ring-opening of ester-activated cyclobutane epoxides or aziridines were utilized to generate 1,3-dipoles in the above described methodologies.[2] Interestingly, the synthesis of *syn*-facially bridged [*n*]polynorbornane frameworks has also been achieved using Diels–Alder or 1,3-dipolar cycloaddition reactions.[3] In continuation of our interest[4] to develop the reactivity profile of diazo ketones, we herein report an efficient new stereoselective approach for the synthesis of *syn*-facially bridged norbornane skeletons using rhodium(II)-generated transient carbonyl ylide methodology.[5,6]

We envisaged that the substituted norbornene derivatives could serve as one building block and carbonyl ylides derived from α-diazo ketones could act as the other. The new construction tactic lends itself to the assembly of complex molecular frameworks with inbuilt functional groups. It was of interest to us to consider the possible pathways (*exo*, *endo*, *syn*, *anti*) with respect to the norbornene derivative **1** by which carbonyl ylides **2** derived from α-diazo ketones could undergo 1,3-dipolar cycloadditions to afford products (Scheme 1). The following illustration shows the many possibilities for the approach of unsymmetrical dipole **2** to dipolarophile **1**. In order to understand the reactivity profile of carbonyl ylides with dipolarophiles like **1**, we carried out reactions involving various norbornene systems as dipolarophiles.

The required starting materials, α-diazo ketones[7] and norbornene dipolarophiles were assembled according to literature methods.[8] Initially, we investigated the rhodium(II)-catalyzed reaction of α-diazo carbonyl compound **3a** and dipolarophile **4** with 0.5 mol% of rhodium(II) acetate dimer as catalyst. The reaction was monitored by TLC until the disappearance of α-diazo carbonyl compound **3a**. Column chromatographic purification of the crude reaction mixture provided the cycloadduct **5a** in 81% yield (Scheme 2). FT-IR, ^{1}H, ^{13}C NMR and DEPT-135 spectra of the cycloadduct **5a** clearly revealed the formation of an interesting oxabicyclo[2.2.1]heptane fused norbornane system via the cycloaddition of carbonyl ylide with bicyclic alkene **4** in a stereoselective manner. The stereochemical assignment and *exo*-addition of carbonyl ylide **2a** to norbor-



Scheme 1.

Keywords: carbonyl ylides; diazo ketones; dipolar cycloadditions; polynorbornanes; rhodium(II) acetate dimer.

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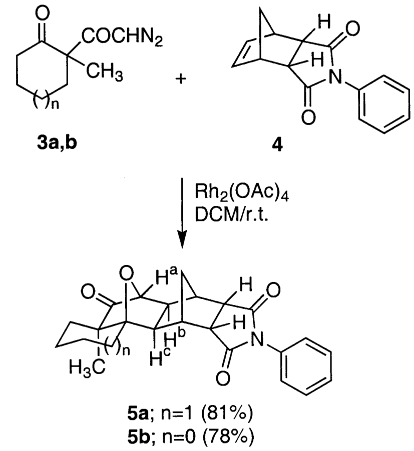
PII: S0040-4039(02)01257-1

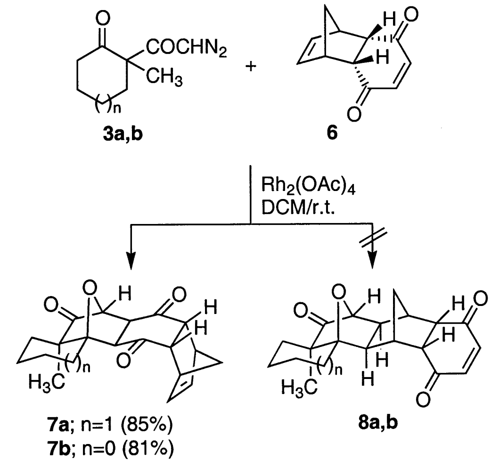


Scheme 2.

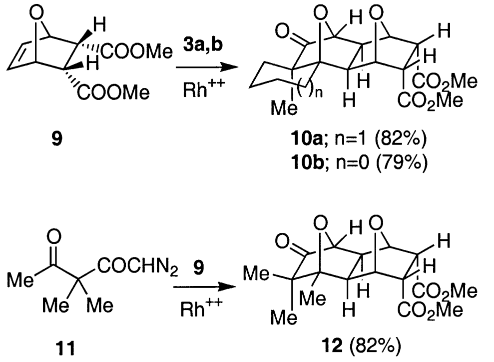
nene **4** was made by inspection of the ^{1}H NMR spectrum. The *exo* and *endo* stereochemistry of the cycloadduct **5a** can easily be distinguished by the coupling constant of H^{a} and H^{b} in the ^{1}H NMR spectrum. The dihedral angle between H^{a} and H^{b} in the *exo* cycloadduct **5a** is close to 90°, meaning that the coupling constant would be very small ($J \approx 0$–2 Hz). The formation of *exo* cycloadduct **5a** was confirmed based on a characteristic singlet resonance signal for the bridgehead (H^{a}) proton. We have not isolated any other isomeric products from the reaction mixture. In a similar manner, product **5b** was obtained in 78% yield using α-diazo ketone **3b** and the alkene **4**.

Next, we performed a similar reaction in the presence of substituted norbornene **6**.[8a] We hoped that the carbonyl ylide **2** would undergo cycloaddition to both C=C bonds present in dipolarophile **6**. Treatment of diazo ketones **3a** or **3b** with *endo*-tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione **6** in the presence of rhodium(II) acetate dimer (Scheme 3) furnished interesting cycloadducts **7a**[9] (85%) and **7b** (81%), with complete stereoselectivity. Carbonyl ylide **2** underwent cycloaddition only with the electron deficient C=C bond of the quinone moiety. The formation of other expected products **8a**,**b** (C=C addition) was not observed. We did not observe[10] any products as a result of cycloaddition of carbonyl ylide **2** to the C=O groups of the quinone moiety.

Encouraged by these results, we next investigated the reactions of carbonyl ylides with 7-oxanorbornene derivative **9**[8b] to obtain *syn*-facially bridged polyoxanorbornane systems. Thus, treatment of α-diazo ketones **3a**,**b** and **11** with dipolarophile **9** in the presence of Rh$_2$(OAc)$_4$ furnished the novel cycloadducts **10a**,**b** and **12**[11] in 82, 79 and 82% yields, respectively (Scheme 4). The structures of cycloadducts **10a**,**b**/**12** were established based on their interrelated spectral data. Moreover, the stereochemistry and *exo*-cycloaddition of carbonyl ylides with 7-oxanorbornene systems were unequivocally corroborated based on the single-crystal X-ray analysis[12] of the cycloadduct **10a**.

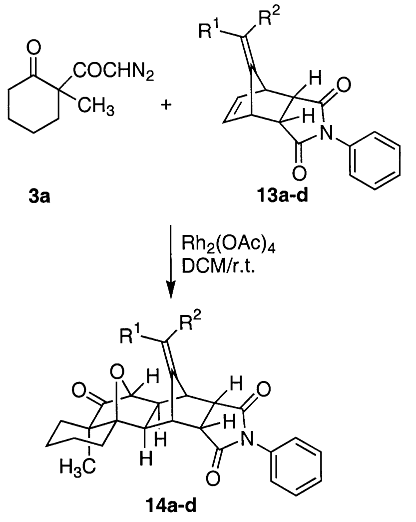


Scheme 3.



Scheme 4.

In order to increase the complexity in the norbornene dipolarophiles, we synthesized[8c] norbornene derivatives **13a**–**d** starting from fulvenes. Treatment of α-diazo ketone **3a** with **13a** in the presence of Rh$_2$(OAc)$_4$ provided the cycloadduct **14a** in 79% yield. Similarly, reactions of α-diazo ketone **3a** with **13b**–**d** were carried out to afford the corresponding products **14b**–**d** in good yields (Scheme 5, Table 1).



Scheme 5.

Table 1. Reaction of α-diazo carbonyl compound **3a** with norbornene derivatives **13a**–**d**

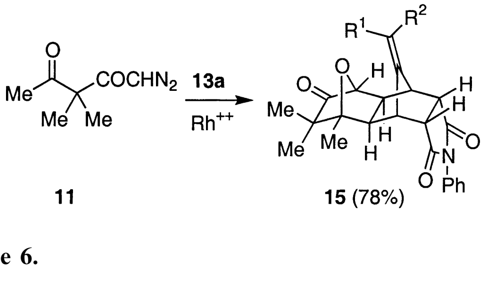
Entry	R^1	R^2	Time (h)	Yields[a] of **14**/%
a	H	4-$CH_3C_6H_4$	4	79
b	H	4-$CH_3C_6H_4$	3.5	82
c	H	4-ClC_6H_4	4	79
d	-CH_2-CH_2-CH_2-CH_2-		3.5	84

[a] Yields (unoptimized) refer to isolated pure compounds **14a**–**d**.

Finally, we carried out a similar reaction using diazo ketone **11** with norbornene derivative **13a** in the presence of rhodium(II) acetate dimer, which also afforded a cycloadduct, **15**, in 78% yield stereoselectively (Scheme 6). These reactions also revealed that the carbonyl ylide underwent the preferred cycloaddition with norbornene derivatives **13a**–**d** in a chemoselective manner. The rhodium(II)-generated transient carbonyl ylides did not react with the exocyclic olefin functional group present in norbornene derivatives **13a**–**d**. The *exo*-cycloaddition of carbonyl ylide to **13a**–**d** and the proposed structures of products **14a**–**d**, and **15** were established based on similarities with the spectral data of other products described herein.

In all these reactions, the exclusive products were *exo*-cycloadducts of complex oxygen-containing *syn*-facially bridged norbornane frameworks. Moreover, cycloaddition reactions were found to be highly stereoselective and afforded functionalized *syn*-facially bridged [2.2.1]-ring systems in good yields via tandem cycloaddition–cyclization reactions. Starting from relatively simple precursors, these reactions resulted in the formation of four chiral centers and two new C–C bonds in a stereoselective manner.

In summary, an efficient stereoselective method to synthesize *syn*-facially bridged norbornane frameworks has been developed using a tandem cyclization–cycloaddition process in the presence of $Rh_2(OAc)_4$ catalyst. Moreover, these cyclic systems are suitable for further diverse transformations to obtain complex carbocyclic molecules. Further elaborate studies on facial selectivity of the reactions of carbonyl ylides including theoretical aspects are currently in progress.



11 **15** (78%)

Scheme 6.

Acknowledgements

This research was supported by Young Scientist Scheme, CSIR, New Delhi. We thank Dr. P. K. Ghosh, Director and Dr. R. V. Jasra, Head of the discipline for their encouragement shown in this work. S.A.B. and C.G. thank CSIR, New Delhi, for a Fellowship.

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9. All new compounds gave satisfactory spectral data consistent with their structures. Spectral data for compound **7a**: Colorless solid; mp 192–194°C ($CHCl_3$/hexane); ν_{max} (KBr) 2942, 2865, 1765, 1701, 1459, 1306, 1250, 1158, 1001 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.09 (2H, s, =CH), 4.69 (1H, s, OC*H*), 3.52 (1H, dd, $J_1=11.8$ Hz, $J_2=2.6$ Hz), 3.40 (1H, dd, $J_1=11.8$ Hz, $J_2=2.6$ Hz), 3.29 (2H, s), 2.91 (1H, d, $J=8.7$ Hz), 2.77 (1H, d, $J=8.7$ Hz), 1.81–1.16

(10H, m), 1.08 (3H, s, CH_3); δ_C (50.3 MHz, $CDCl_3$) 212.5 (C=O), 207.8 (C=O), 206.5 (C=O), 137.4 (=*C*H), 137.2 (=*C*H), 92.5 (*quat*-C), 84.9 (O*C*H), 57.9 (*C*H), 55.5 (*C*H), 55.3 (*C*H), 53.2 (*C*H), 51.4 (*quat*-C), 46.9 (CH_2), 44.4 (*C*H), 31.0 (CH_2), 26.2 (CH_2), 22.2 (CH_2), 20.2 (CH_2), 17.0 (CH_3); MS (FD^+): *m*/*z* 326 (M^+). Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.73; H, 6.76%.

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11. Spectral data for compound **12**: Colorless solid, mp 155–157°C; IR (KBr): ν_{max} 2984, 2966, 1744, 1435, 1377, 1358, 1270, 1230, 1008, 947, 815 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.02 (s, 1H, OC*H*), 4.93 (s, 1H, OC*H*), 4.39 (s, 1H, OC*H*), 3.65 (s, 6H, OCH_3), 3.07 (d, 1H, $J=9.6$ Hz), 2.99 (d, 1H, $J=9.6$ Hz), 2.34 (d, 1H, $J=6.6$ Hz), 2.13 (d, 1H, $J=6.6$ Hz), 1.45 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.99 (s, 3H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.1 (CH_3), 19.3 (CH_3), 20.8 (CH_3), 47.6 (CH), 49.8 (CH), 51.9 (CH), 52.1 (CH), 52.3 (OCH_3), 79.2 (OCH), 81.9 (OCH), 83.8 (OCH), 89.0 (*quat-C*), 171.1 (COO), 171.4 (COO), 216.4 (C=O); MS (FD^+): *m*/*z* 338 (M^+). Anal. calcd for $C_{17}H_{22}O_7$: C, 60.35; H, 6.55. Found: C, 60.44; H, 6.59%.
12. The X-ray crystal structure analysis of compound **10a** will be reported elsewhere.