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The Baylis–Hillman acetates in organic synthesis: development of a facile strategy for synthesis of functionalized unsaturated benzo-fused macrocyclic ethers and [*n*] metacyclophanes†

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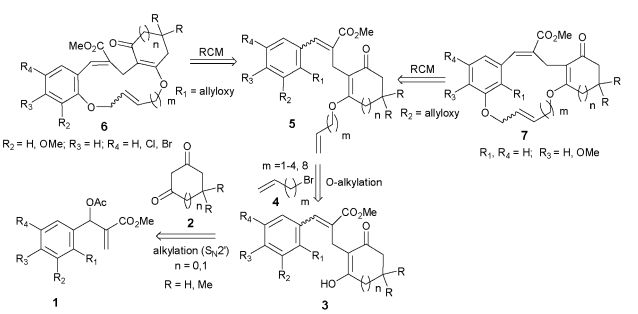
A general synthetic protocol for obtaining functionalized unsaturated benzo-fused macrocyclic ethers and [*n*] metacyclophanes containing 13-, 14-, 15-, 16- and 20-membered rings has been developed using Baylis–Hillman (BH) acetates as starting materials and ring closing metathesis as a key step.

Development of simple and facile strategies for synthesis of large ring (>12-membered) compounds continues to attract the attention of synthetic chemists.[1] This is because of two main reasons 1) *some important marketed drugs have such structural features*, 2) *challenges and opportunities involved in developing simple and facile strategies for their synthesis*.[1] Cyclophanes belong to a unique class of macrocycles containing bridged aromatic groups and exhibit important properties such as molecular recognition and catalysis.[2] Therefore there has been, in recent years, increasing interest in the development of convenient synthetic methodologies for obtaining these structural frame-works.[1c–e,2,3] In continuation of our interest in the synthesis of heterocyclic and carbocyclic molecules[4] using the Baylis–Hillman (BH) adducts/derivatives we herein report a general protocol for obtaining functionalized unsaturated benzo-fused macrocyclic ethers and [*n*] metacyclophanes.

The Baylis–Hillman reaction[5,6] has indeed become a reaction of choice for obtaining diverse classes of densely functionalized molecules which have been utilized in many organic transformations and also in the synthesis of various biologically active molecules. Based on our vast experience in the area of Baylis–Hillman reaction and its applications we planned the retro-synthetic strategy for obtaining unsaturated benzo-fused macrocyclic ethers and [*n*] metacyclophanes as shown in Scheme 1. Accordingly we focussed our attention for preparation of desired diene **5a** (Table 1, Entry 1). We have thus performed alkylation of **2a** (dimedone) with methyl 3-acetoxy-3-(2-allyloxyphenyl)-2-methylenepropanoate (**1a**; acetatate of BH alcohol obtained from 2-allyloxybenzaldehyde and methyl acrylate) and then *O*-alkylation of the *in situ* resulting product **3a** with allyl bromide **4a** to obtain **5a**. Best results in this direction were obtained when we treated BH-acetate **1a** (2 mmol) with **2a** (2 mmol) in the presence of K_2CO_3 (2 mmol) in DMF (3 mL) at room temperature for 6 h. The *in situ* resulting product **3a**, on treatment with allyl bromide **4a** (10 mmol) in the presence of K_2CO_3 (2 mmol) at room temperature for 4 h provided the required diene **5a** (*E*-selectivity 95%) in 68% (for two steps) yield (Table 1, Entry 1).

Attempted ring closing olefin metathesis (RCM)[7] reactions of **5a** with Grubbs' first generation catalyst as well as with Grubbs' second generation catalyst were not successful. However, we have obtained encouraging results using $Ti(O^iPr)_4$ (20 mol%) as co-catalyst.[8] Thus treatment of **5a** (0.5 mmol) with Grubbs' first generation catalyst (3 mol%) in the presence of $Ti(O^iPr)_4$ (20 mol%) in dichloromethane (DCM) under high dilution at reflux temperature for 4 h provided **6a** [(4*E*,15*E*)-10,10-dimethyl-2,7-dioxa-15-methoxycarbonyltricyclo[15.4.0.0^{8,13}]henicosane-1(17),4,8(13),15,18,20-hexaen-12-one] after usual workup followed by column chromatography and crystallization of the resulting solid



Scheme 1 Retro-synthetic strategy for synthesis of unsaturated benzo-fused macrocyclic ethers and [*n*] metacyclophanes.

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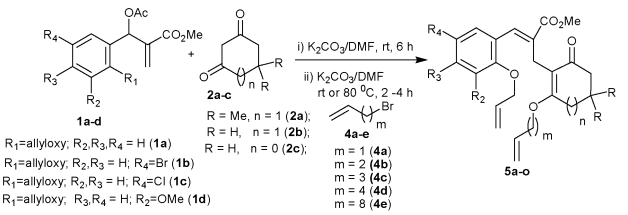
† Electronic supplementary information (ESI) available: Representative experimental procedure, with all spectral data of **5a–x**, **6a–o**, **7a–i**, crystal data and ORTEP diagram of **6a**, **6c** (*E* & *Z*), **6k**, **6m**, **6n**, **6o**, **7a** (*E* & *Z*) and **7g**. CCDC **6a** (CCDC # 914817), **6c–*E*** (CCDC # 914818), **6c–*Z*** (CCDC # 914819), **6k** (CCDC # 917199), **6m** (CCDC # 915410), **6n** (CCDC # 917200), **6o** (CCDC # 915411), **7a–*E*** (CCDC # 915412), **7a–*Z*** (CCDC # 917201) and **7g** (CCDC # 915413). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra40926k

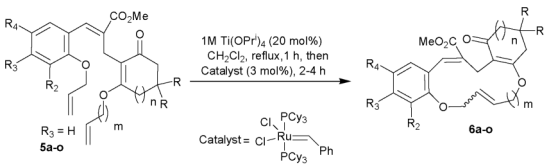
Table 1 Synthesis of dienes **5a–o** *via* the reaction of **1a–d** with **2a–c** followed by treatment of the resulting mono-alkylated cyclic-1,3-diones with alkenyl bromides, **4a–e**[a]



Entry	Acetate	Dione	Bromide	Product[b]	Yield (%)
1	**1a**	**2a**	**4a**	**5a**[c]	68
2	**1a**	**2b**	**4a**	**5b**[c]	67
3	**1a**	**2c**	**4a**	**5c**	58
4	**1b**	**2a**	**4a**	**5d**	56
5	**1b**	**2b**	**4a**	**5e**[d]	62
6	**1c**	**2a**	**4a**	**5f**[c]	66
7	**1c**	**2b**	**4a**	**5g**	62
8	**1d**	**2a**	**4a**	**5h**[c]	57
9	**1d**	**2b**	**4a**	**5i**[d]	62
10	**1d**	**2c**	**4a**	**5j**[c]	65
11	**1a**	**2a**	**4b**	**5k**[e]	56
12	**1a**	**2b**	**4b**	**5l**[e]	60
13	**1a**	**2c**	**4c**	**5m**[c]	64
14	**1a**	**2c**	**4d**	**5n**	65
15	**1a**	**2c**	**4e**	**5o**[d]	67

[a] All reactions were carried out on 2 mmol scale of BH-acetate (**1a–d**) with 2 mmol of dione (**2a–c**) in the presence of K_2CO_3 (2 mmol) in DMF at room temperature followed by treatment of the resulting products with alkenyl bromide **4a–e** (4 or 10 mmol) in the presence of K_2CO_3 (2 mmol) at room temperature or 80 °C. [b] All compounds were fully characterized (see ESI). [c] These compounds contain minor *Z*-isomer (3–5%). [d] These compounds contain minor *Z*-isomer (6–7%). [e] **5k** contains 20% while **5l** has 15% corresponding minor *Z*-isomer (see ESI).

Table 2 Synthesis of unsaturated benzo-fused macrocyclic ethers **6a–o** *via* ring closing olefin metathesis of **5a–o**[a,10,12]



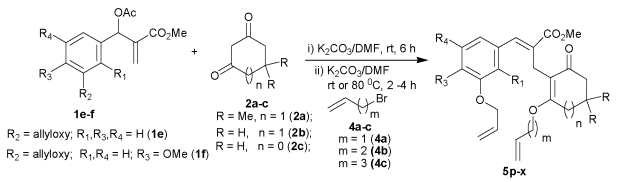
Entry	Diene	R_2	R_4	R	*n*	*m*	Product[b]	Yield (%)
1	**5a**	H	H	Me	1	1	**6a**[c]	70[d]
2	**5b**	H	H	H	1	1	**6b**	63[d]
3	**5c**	H	H	H	0	1	**6c**[c]	53(*E*) + 35(*Z*)[e]
4	**5d**	H	Br	Me	1	1	**6d**	61[d]
5	**5e**	H	Br	H	1	1	**6e**	58[d]
6	**5f**	H	Cl	Me	1	1	**6f**	68[d]
7	**5g**	H	Cl	H	1	1	**6g**	61[d]
8	**5h**	OMe	H	Me	1	1	**6h**	56[d]
9	**5i**	OMe	H	H	1	1	**6i**	59[d]
10	**5j**	OMe	H	H	0	1	**6j**	48(*E*) + 30(*Z*)[e]
11	**5k**	H	H	Me	1	2	**6k**[c]	70[d]
12	**5l**	H	H	H	1	2	**6l**	78[d]
13	**5m**	H	H	H	0	3	**6m**[c]	82[f]
14	**5n**	H	H	H	0	4	**6n**[c]	91[f]
15	**5o**	H	H	H	0	8	**6o**[c]	85[d]

[a] All reactions were carried out on 0.5 mmol scale of diene (**5a–o**) with Grubbs' first generation catalyst (3 mol%) and $Ti(O^iPr)_4$ (20 mol %) in dichloromethane under high dilution at reflux temperature. [b] All compounds were fully characterized (see ESI). [c] Structures of these compounds were further confirmed by single crystal X-ray data analysis.[9] [d] Only (*E*)-isomer is isolated.[10,11] [e] (*E*)- & (*Z*)- isomers were isolated by column chromatography.[11] [f] Only (*Z*)- isomer is isolated.[11]

[containing minor (4*Z*)-isomer (≈10%)] (from 40% ethyl acetate in hexanes) in 70% yield (Table 2, entry 1). Structure of the molecule **6a** was further confirmed by single-crystal X-ray data analysis[9] (see ESI†). Encouraged by this result we have prepared various dienes **5b–o** from the BH-acetates **1a–d**, cyclic-1,3-diones **2a–c**, and alkenyl bromides **4a–e** following the similar reaction sequence used for **5a** in 56–68% isolated yields (Table 1).

To examine the generality of this strategy we subjected the dienes **5b–o** to RCM reaction under similar conditions as in the case of **5a** (Table 2, entry 1) to provide unsaturated benzo-fused macrocyclic ethers **6b–o** containing 13-, 14-, 15-, 16-, and 20-membered rings in 56–91% isolated yields (Table 2, entries 2–15). Macrocyclic compounds ($n = 1$ and $m = 1$) (**6a**, **6b**, **6d**, **6e**, **6f**, **6g**, **6h**, and **6i**)[10] were obtained as (*E*)-isomers[11] after column chromatography followed by re-crystallization (from ethyl acetate and hexanes mixture). In the case of compounds **6c** and **6j** ($n = 0$ and $m = 1$) we could isolate both (*E*)- & (*Z*)-isomers[11] (separated by column chromatography). Structures of both (*E*)- & (*Z*)-isomers[11] of **6c** were also confirmed by single-crystal X-ray data analysis.[9] Stereochemistry of (*E*)- & (*Z*)-isomers[11] of **6j** is assigned in comparison of their NMR spectral data with that of (*E*)- & (*Z*)-isomers of **6c**. We obtained the compounds **6k**, **6l** ($n = 1$, $m = 2$) and **6o** ($n = 0$, $m = 8$) as (*E*)-isomers while molecules **6m** ($n = 0$, $m = 3$) and **6n** ($n = 0$, $m = 4$) were isolated as (*Z*)-isomers after column chromatography followed by re-crystallization (see ESI†). Structures and stereochemistry of compounds **6k**, **6m–o** were further confirmed by single-crystal X- ray data analysis.[9,10] After successful synthesis of tricyclic compounds with middle ring as a macrocycle, we directed our attention towards synthesis of [*n*] metacyclophanes. Accordingly we prepared the required dienes **5p–x** from **1e–f** (BH acetates), cyclic-1,3-diones **2a–c**, and alkenyl bromides **4a–c** following the similar procedure used for **5a** (Table 3, entries 1–9). RCM reactions of **5p–x** were performed as in the case of **5a** to afford the corresponding [*n*] metacyclophanes **7a–i** containing 14-, 15-, and 16-membered rings (Table 4, entries 1–9) in 70–90% yields. It is interesting to note that metacyclophanes **7a–e** ($n = 0$, 1, $m = 1$) were obtained as mixture of (*E*)- and (*Z*)-isomers (separated by column chromatography). However metacyclophanes **7f–i** ($n = 0$,1; $m = 2$,3) were isolated as (*E*)-isomers after column chromatography followed by re-crystalization (see ESI†). Structures of **7g** and both (*E*)- & (*Z*)-isomers of **7a** were further confirmed by single-crystal X-ray data analysis.[9,11] In the ^{1}H NMR spectrum of (*E*)-**7a** one of the aromatic protons (probably Ha) appeared at δ 6.67 while the same proton in (*Z*)-isomer appeared at δ 7.39. In the ^{13}C NMR spectrum of (*E*)-**7a** allyloxy carbons (C_3 & C_6) appeared at δ 66.97 & 69.03 where as these carbons in the (*Z*)-

Table 3 Synthesis of dienes **5p–x** *via* the reaction of **1e–f** with **2a–c** followed by treatment of the resulting mono-alkylated cyclic-1,3-diones with alkenyl bromides **4a–c**[a]

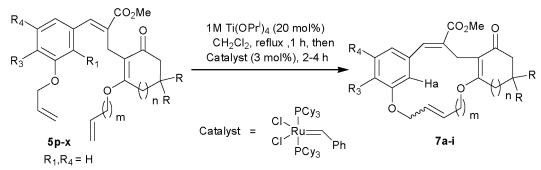


Entry	Acetate	Dione	Bromide	Product[b]	Yield (%)
1	**1e**	**2a**	**4a**	**5p**[c]	63
2	**1e**	**2b**	**4a**	**5q**[c]	69
3	**1e**	**2c**	**4a**	**5r**[c]	52
4	**1f**	**2b**	**4a**	**5s**[c]	63
5	**1f**	**2c**	**4a**	**5t**[c]	67
6	**1e**	**2a**	**4b**	**5u**	58
7	**1e**	**2b**	**4b**	**5v**	62
8	**1e**	**2b**	**4c**	**5w**[c]	61
9	**1e**	**2c**	**4c**	**5x**[c]	69

[a] All reactions were carried out on a 2 mmol scale of BH acetates (**1e–f**) following similar procedure as in **5a–o**. [b] All compounds were fully characterized (see ESI). [c] These contain minor *Z*-isomer (3–5%) (see ESI).

isomer appeared at δ 61.83 & 65.14. Similarly in ^{1}HNMR spectra of (*E*)-**7b–e** one of the aromatic protons (probably Ha) appeared between δ 6.57–6.72 while the same proton in (*Z*)-**7b–e** appeared between δ 7.32–7.63. In the ^{13}C NMR spectra of allyloxy carbons (C_3 & C_6) of (*E*)-**7b–e** appeared between δ 66.86–68.28 & 68.75–70.15 where as these carbons appeared between δ 61.97–63.47 & 64.74–65.82 in the case of (*Z*)-**7b–e**.

Table 4 Synthesis of unsaturated [*n*] metacyclophanes **7a–i** *via* ring closing metathesis of **5p–x**[a10,11]



Entry	Diene	R_3	R	*n*	*m*	Product[b]	Yield (%)
1	**5p**	H	Me	1	1	**7a**[c]	56(*E*) + 27(*Z*)[d]
2	**5q**	H	H	1	1	**7b**	58(*E*) + 32(*Z*)[d]
3	**5r**	H	H	0	1	**7c**	48(*E*) + 31(*Z*)[d]
4	**5s**	OMe	H	1	1	**7d**	53(*E*) + 33(*Z*)[d]
5	**5t**	OMe	H	0	1	**7e**	48(*E*) + 28(*Z*)[d]
6	**5u**	H	Me	1	2	**7f**	70[e]
7	**5v**	H	H	1	2	**7g**[c]	79[e]
8	**5w**	H	H	1	3	**7h**	81[e]
9	**5x**	H	H	0	3	**7i**	85[e]

[a] All reactions were carried out on a 0.5 mmol scale of diene (**5p–x**) with Grubbs' catalyst following a similar procedure as in the case of **6a–o**. [b] All compounds were fully characterized (see ESI). [c] Structures were further confirmed by single crystal X-ray data analysis.[9] [d] Both (*E*)- and (*Z*)-isomers were isolated.[11] [e] Only (*E*)-isomer is isolated.[10,11]

In summary, we have developed a convenient protocol for synthesis of benzo-fused macrocyclic ethers and metacyclophanes thus further demonstrating the importance of Baylis–Hillman acetates as useful synthons in organic synthesis.

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9 Detailed X-ray crystallographic data is available from the CCDC, Cambridge (UK) for compounds **6a** (CCDC # 914817), **6c–*E*** (CCDC # 914818), **6c–*Z*** (CCDC # 914819), **6k** (CCDC # 917199), **6m** (CCDC # 915410), **6n** (CCDC # 917200), **6o** (CCDC # 915411), **7a–*E*** (CCDC # 915412), **7a–*Z*** (CCDC # 917201) and **7g** (CCDC # 915413).

10 (*E*)-Stereochemistry of double bond in **6b**, **6d–i** and **6l** (after RCM reaction) was assigned in comparison of chemical shift values of allyloxy carbons (^{13}CNMR) with that of **6a** and **6k**. (*E*)-Stereochemistry in **7f**, **h**, **i** was assigned in comparison of chemical shift values of allyloxy carbons with that of **7g**.

11 (*E*)- and (*Z*)-Stereochemistry refers to the newly formed double bond after RCM reaction.

12 Sinceall the dienes **5a–x** (except **5k** and **5l**) contain very less quantities of minor (*Z*)-isomer we did not look for the corresponding macrocyclic compounds in RCM reactions. In the case of **5k** and **5l** we could not isolate any macrocyclic compounds corresponding to minor (*Z*)-isomer, probably minor (*Z*)-isomers did not participate in RCM reaction.

