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A tandem Heck reaction leading to a 26-membered carbocycle

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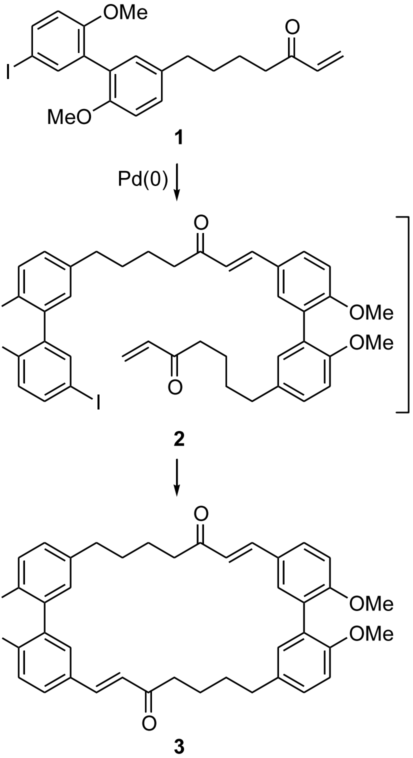
Abstract—Sequential inter- and intramolecular Heck reactions have been used to construct a 26-membered carbocycle. This new tandem reaction uses strain effects to advantage in biasing the first step towards intermolecular coupling. In the second step, the lack of strain in the formation of a large ring promotes this course over polymerisation. © 2002 Elsevier Science Ltd. All rights reserved.

Intramolecular Heck reactions have been used to prepare all manner of different ring systems, with closures to form ring sizes from 3 to 24 having been demonstrated.[1] One area that has witnessed only sporadic attention is macrocyclisation.[2–7] Indeed, since the pioneering work of Ziegler et al. was reported in 1981, very few extensions have been reported.[2]

Stocks et al. used the method to prepare a number of analogues of FK-506.[3] Lactones comprising of 18, 20 and 22 atoms were prepared in yields up to 29, 24 and 42%, respectively. Ma and Negishi achieved greater efficiency in Heck-type cyclisations of ω-haloallenes.[4] Indeed, one 20-membered carbocycle was given in a remarkable 86% yield. In the same study an attempted 13-*endo*-trig cyclisation to an unactivated alkene gave only 18% of the cyclisation product with reduced starting material accounting for 37% of the outstanding mass balance (dimers and higher oligomers were presumed to account for much of the remainder). To overcome this tendency for intermolecular coupling reactions to compete with macrocyclisation, Hauske et al. immobilised a series of ω-haloalkenes on a solid support. In this way good to excellent product yields could be achieved for targets containing 20–24-membered rings.[5]

It appeared to us that a substrate such as **1** was unlikely to give a 13-membered ring on treatment with Pd(0) as cyclisation would require a build up of strain during the course of the reaction.[7,8] Thus, intermolecular coupling to **2** was likely to dominate. For the cyclisation of **2** to **3**, however, strain would be less of an issue. As a consequence, macrocyclisation might compete effectively with further intermolecular coupling reactions leading to a successful tandem sequence (Scheme 1). Herein, we report the results of that study.

Our synthesis of precursor **1** began with biphenol **4**. All attempts to effect the monoiodination of **4** led to complex product mixtures. By contrast, monomethyla-



Scheme 1.

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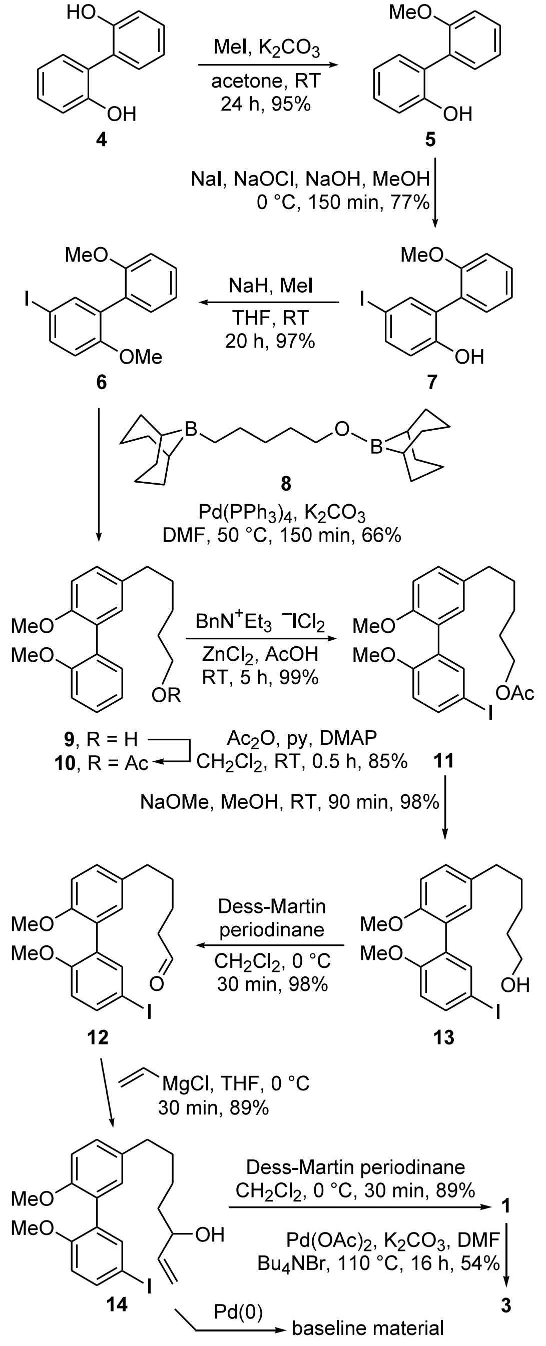
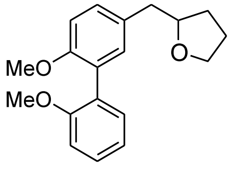
tion was readily accomplished using methyl iodide and provided biaryl **5** in 95% yield. Selective iodination of the phenol could then be accomplished using sodium iodide and sodium hypochlorite in basified methanol.[9] Protection of iodophenol **7** as its methyl ether **6**, was followed by a *B*-alkyl Suzuki coupling with organoborane **8** (prepared in situ by treatment of 4-pentenol with 2 equiv. of 9-BBN).[10]

The direct iodination of **9** to **13** proved troublesome. Many literature methods were examined but to no avail. One side reaction of note was the formation of tetrahydrofuran **15** when **9** was heated in acetonitrile with NIS. This indicated a need to protect the alcohol function. Successive acetylation (to **10**), iodination (to **11**)[11] and deprotection steps each proceeded smoothly and in near quantitative yields to give alcohol **13**. A Dess–Martin periodinane oxidation then gave aldehyde **12**, which was transformed into allylic alcohol **14** on exposure to vinylmagnesium chloride (Scheme 2).



Scheme 2.



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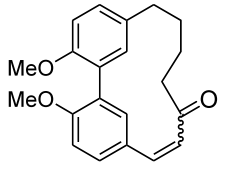

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Attempts to effect a palladium-mediated macrocyclisation and/or dimerisation of **14** led to a myriad of polar products. Partial separation of these products could be achieved by column chromatography. Analysis of a number of fractions showed that each displayed similar NMR characteristics, with the more polar fractions showing significant peak broadening. From this we inferred that polymerisation was outpacing macrocyclisation in this case.

In the hope of accelerating macrocyclisation relative to intermolecular coupling, **14** was oxidised to **1** with the Dess–Martin periodinane reagent. Pleasingly, when **1** was treated under standard Heck conditions, using high dilution and with tetrabutylammonium bromide as an accelerant,[12] *trans,trans*-**3** was furnished in 54% yield.[13] While some formation of higher oligomers was evident from analysis of the crude reaction mixture, we were unable to detect the presence of enone **16**. That this was not formed demonstrates the extent to which strain effects may be exploited, allowing sequential inter- and intramolecular Heck coupling reactions to be realised in good yield.[7]

In conclusion, a 26-membered carbocycle has been successfully synthesised in good yield using a tandem Heck reaction. No products arising from 13-ring closure could be detected in cyclisations of either allylic alcohol **14** or enone **1**. The influences of strain, and the value of using an activated olefin to bias reactions in favour of large ring closure, have both been demonstrated.

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References

1. (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151; (b) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer: Berlin, 1980; (c) Heck, R. F. *Org. React.* **1982**, *27*, 345–390; (d) Heck, R. F. In *Fundamental Research in Organometallic Chemistry*; Tsutsui, M.; Ishii, Y.;

Yaozeng, H., Eds.; Van Nostrand Reinhold: New York, 1982; pp. 447–462; (e) Heck, R. F. In *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; (f) Davies, G. D.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433–1445; (g) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 4, pp. 833–863; (h) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, 1991; Vol. 8, pp. 854–883; (i) Overman, L. E.; Abelman, M. M.; Kucera, D. J.; Tran, V. D.; Ricca, D. J. *Pure Appl. Chem.* **1992**, *64*, 1813–1819; (j) Hegedus, L. S. In *Organic Synthesis with Transition Metals*; University Science Books: Mill Valley, 1994; (k) Hegedus, L. S. In *Organometallics in Synthesis—A Manual*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp. 383–459; (l) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423–1430; (m) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411; (n) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7; (o) Tsuji, J. In *Palladium Reagents and Catalysts-Innovations in Organic Synthesis*; Wiley: Chichester, 1995; (p) Soderberg, B. J. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Ed.; Pergamon: Oxford, 1995; Vol. 12, pp. 241–297; (q) Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; pp. 249–252; (r) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393; (s) Gibson (née Thomas), S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*, 447–471; (t) Shibasaki, M.; Boden, C. O. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395; (u) Bräse, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 99–166; (v) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 231–269.

2. Ziegler, F. E.; Chakraborty, U. R.; Weissenfield, R. B. *Tetrahedron* **1981**, *37*, 4035–4040.
3. Stocks, M. J.; Harrison, R. P.; Teague, S. J. *Tetrahedron Lett.* **1995**, *36*, 6555–6558.
4. Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345–6357.
5. Hiroshige, M.; Hauske, J. R.; Zhou, P. *J. Am. Chem. Soc.* **1995**, *117*, 11590–11591. See also (b) Akaji, K.; Kiso, Y. *Tetrahedron Lett.* **1997**, *38*, 5185–5188.
6. (a) Casachi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron Lett.* **1996**, *37*, 4413–4416; (b) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640.
7. While this paper was under review, a similar tandem Heck sequence was reported leading to dehydrophenylalanine cyclophanes. See: Gibson (née Thomas), S. E.; Jones, J. O.; Kalindjian, S. B.; Knight, J. D.; Steed, J. W.; Tozer, M. J. *Chem. Commun.* **2002**, 1938–1939.
8. Dansou, B.; Pichon, C.; Dhal, R. *Eur. J. Org. Chem.* **2000**, 1527–1533.
9. Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287–5291.
10. (a) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp. 49–97; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
11. Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Watanabe, M.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Chem. Lett.* **1988**, 795–798.
12. (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670; (b) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289.
13. Data for **3**: **IR** ν_{max} (neat) 2932 (m), 1678 (s), 1610 (w), 1502 (s), 1483 (s), 1242 (s) cm^{-1}; **UV** λ_{max} (ε_{max}, CH_2Cl_2) 308 (37400), 217 (35000) nm; ^{1}**H NMR** δ_H (300 MHz, $CDCl_3$) 7.56 (2H, d, *J* 16.2 Hz, 2×C*H*), 7.54 (2H, dd, *J* 8.5, 2.4 Hz, 2×Ar*H*), 7.48 (2H, d, *J* 2.4 Hz, 2×Ar*H*), 7.14 (2H, dd, *J* 8.2, 2.4 Hz, 2×Ar*H*), 7.03 (2H, d, *J* 2.1 Hz, 2×Ar*H*), 6.97 (2H, d, *J* 8.7 Hz, 2×Ar*H*), 6.87 (2H, d, *J* 8.5 Hz, 2×Ar*H*), 6.67 (2H, d, *J* 16.2 Hz, 2×C*H*), 3.83 (6H, s, 2×OCH_3), 3.76 (6H, s, 2×OCH_3), 2.70 (4H, t, *J* 6.6 Hz, 2×C(O)CH_2), 2.60 (4H, m, 2×ArCH_2), 1.77–1.63 (8H, m, 4×CH_2); ^{13}**C NMR** δ_C (75 MHz, $CDCl_3$) 201.3 (2×*C*), 159.6 (2×*C*), 155.6 (2×*C*), 143.1 (2×*C*H), 134.7 (2×*C*), 131.9 (2×*C*H), 131.2 (2×*C*H), 129.4 (2×*C*H), 129.3 (2×*C*), 129.2 (2×*C*H), 127.4 (2×*C*), 127.2 (2×*C*), 125.0 (2×*C*H), 111.4 (2×*C*H), 111.1 (2×*C*H), 56.1 (4×*C*H_3), 40.1 (2×*C*H_2), 35.1 (2×*C*H_2), 32.0 (2×*C*H_2), 24.8 (2×*C*H_2); **HRMS** found $[2M+Na]^+$: 1311.6161, $C_{84}H_{88}O_{12}Na$ requires 1311.6162. Found $[M+Na]^+$: 667.3027, $C_{42}H_{44}O_6Na$ requires 667.3030.