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Stereoselective synthesis of tetralins using cationic cyclisations

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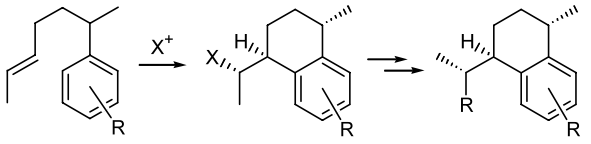
Abstract—Tetralins, including the terpene calamenene, were prepared by 6-*endo* cationic cyclisations, effected by addition of an I(I) reagent to alkenylarenes, followed by reductive deiodination. An activating group on the arene was required for efficient cationic cyclisation. Good diastereoselectivity, relative to a chiral centre in the chain linking the alkene to the arene, was observed, with *Z*-alkenes giving predominantly 1,4-*cis* disubstituted tetralins, and *E*-alkenes giving predominantly 1,4-*trans* derivatives. Analogous 6-*exo* cationic cyclisations proved very limited in scope.

We became interested in the possibility of preparing 1,4-disubstituted tetralins by carrying out diastereoselective cationic cyclisations, initiated by addition of some heteroatom electrophile X^+ to alkenes, and terminated by electrophilic attack on arenes (Scheme 1). Nucleophilic substitution of the heteroatom function X would then provide a flexible route to several families of terpenes, including the cadinenes,[1] and the pseudopterosins, which have potent anti-inflammatory activity.[2] A particular attraction of this route was the use of simple precursors, which could be prepared in enantiopure form.

Relatively little work has been reported on cationic alkene–arene cyclisations of the type shown in Scheme 1, and almost nothing is known concerning diastereoselectivity in these reactions. Epoxides have been employed as initiators,[3] but it was not obvious how diastereoselectivity, relative to existing chiral centres in the chain linking the alkene to the arene, could be achieved. Activation of the alkene by episulfonium ion formation is a method of wide scope, but it gives very poor diastereoselectivity.[4] Various selenium reagents have also been shown to be effective initiators,[5] as has sulfur trioxide.[6] However, we preferred to study cyclisations initiated by formation of halonium ions, because the products contain a halide, which would allow further C–C bond forming reactions by nucleophilic substitution. Bromine has been used to initiate cationic alkene–arene cyclisations under mild conditions,[7] although competing 1,2-addition was sometimes a drawback.[7b,c] Barluenga overcame this problem by using 'I^+ BF_4^-', formed in situ by addition of HBF_4 to bis(pyridine)iodine(I) tetrafluoroborate at low temperatures.[8] We decided to study Barluenga's method in more detail, (i) to determine if its scope could be extended to the substrates required for terpene synthesis, and (ii) to determine if good diastereoselectivity, in relation to existing chiral centres in the linking chain, could be obtained. The latter aspect had been addressed for bromonium-mediated alkene–arene cyclisations by Finch,[7a] and high diastereoselectivity was found when the alkene bore a phenyl substituent. We now present a series of model studies which show that a variation on this strategy does indeed provide a viable stereoselective route to tetralins.



Scheme 1.

We first studied *exo*-arene–alkene cyclisations, as shown in Scheme 2. The 4-pentenylbenzene **1a** was subjected to cyclisation using Barluenga's conditions.[8] It afforded the desired iodomethyltetralin **2a** in 50% yield (after chromatography), but as a 50:50 mixture of diastereoisomers (Scheme 2). The regioisomer **1b** also underwent selective *6-exo* cyclisation, but again with no diastereoselectivity. We hoped that introduction of a substituent at the terminus of the alkene, which was

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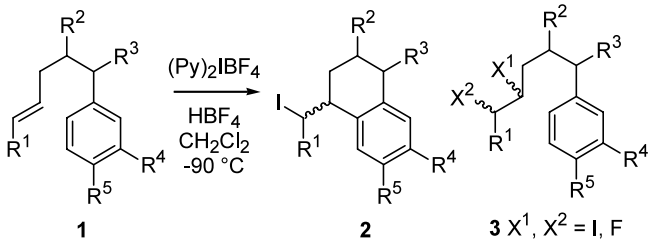


1 **2** **3** X^1, X^2 = I, F

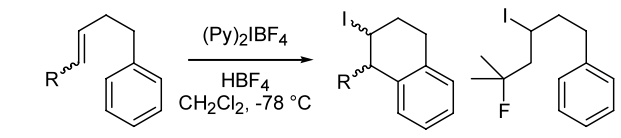
1a, **2a** R^1, R^2, R^4 = H; R^3, R^5 = Me
1b, **2b** R^1, R^3, R^4, R^5 = H; R^2 = Me
1c, **3a** R^1, R^5 = Me; R^2, R^3, R^4 = H
1d, **3b** R^1, R^3, R^5 = Me; R^2, R^4 = H
1e, **3c** R^1, R^3 = Me; R^2, R^5 = H; R^4 = OMe
1f, **3d** R^1, R^3 = Me; R^2, R^5 = H; R^4 = OH

Scheme 2. 6-*exo* Cyclisations.

required for terpene synthesis, might result in improved stereoselectivity. However, the 4-hexenylbenzenes **1c** and **1d** gave no cyclisation products under a variety of conditions, but instead gave mixtures of 1,2-iodofluorination adducts **3a** and **3b**.[9] Electron-donating substituents were introduced onto the ring in an effort to promote cationic cyclisation, but to no avail, exclusive iodofluorination was observed with the methoxy and hydroxy derivatives **1e** and **1f**. These failures were very disappointing and they reveal an unexpected limitation in the scope of the 6-*exo* cationic cyclisations. Moreover, the cyclisations which could be carried out were of little interest, because of their lack of stereoselectivity.

We then decided to investigate a variation, which relied on a *6-endo* cyclisation of 3-alkenylbenzenes (Scheme 3).[8] Gratifyingly, both (*E*)- and (*Z*)-3-pentenylbenzene, **4a** and **5a**, underwent cyclisation, to give *trans*- and *cis*-2-iodo-1-methyltetralins **6a** (60%) and **7a** (43%), respectively, consistent with *anti* addition to the alkene. Worryingly however, increasing the steric bulk at the alkene by replacing the methyl group with an isopropyl (**4b**, **5b**) caused the cyclisation to fail and the tetralins **6b** and **7b** were not formed. The major product was the iodo fluoro compound **8**, presumably formed by a hydride shift in the iodonium ion/carbenium ion, followed by trapping with fluoride from the tetrafluoroborate.

Analogues in which the arene was activated by electron-releasing substituents, and in which a methyl substituent was present in the benzylic position, were then studied. Racemic cyclisation precursors were prepared by a simple two-step sequence (Scheme 4). Copper catalysed conjugate additions of the arylmagnesium bromides to crotonaldehyde, using the excellent procedure of Nakamura,[10] followed by Wittig reactions, and Julia coupling reactions, stereoselectively furnished the desired *Z*- and *E*-alkenes, respectively, in 40–69% yields.



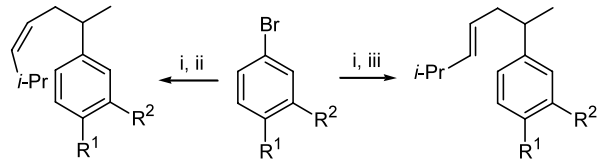
Trans: **4a** R = Me
4b R = *i*-Pr
Cis: **5a** R = Me
5b R = *i*-Pr

Trans: **6a** R = Me
6b R = *i*-Pr
Cis: **7a** R = Me
7b R = *i*-Pr

8

Scheme 3.

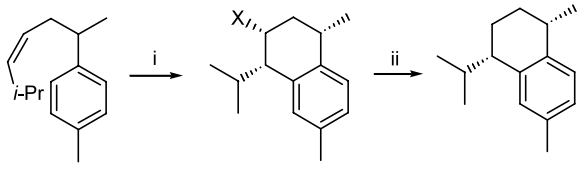
Cationic cyclisation of alkene **9** (ca. 1:5 *E*:*Z*) gave an inseparable mixture of three diastereomers (6:1:1) of iodotetralin **13**, together with unidentified side products (Scheme 5).[11] Even the modest activating effect of the methyl substituent was sufficient to make the cyclisation viable again. The results were somewhat variable, but the best isolated yield of iodotetralins was 41%. The relative stereochemistry of the major product was assigned as **13a** by detailed NMR analysis,[12] and by reduction of the product, as described below. One of the minor diastereomers was the product **13b** derived from the *E*-alkene, and the other was not identified. This result adds to the small number of examples of good diastereoselectivity, relative to the chiral centre in the tether linking the alkene and the arene, in cationic arene–alkene cyclisations.[7a,13] Such selectivity is a pre-



9 R^1 = Me, R^2 = H
10 R^1 = H, R^2 = OMe

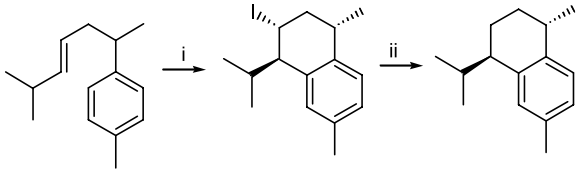
11 R^1 = Me, R^2 = H
12 R^1 = H, R^2 = OMe

Scheme 4. *Reagents and conditions*: (i) Mg, THF; HMPA, 5 mol% $CuBr{\cdot}SMe_2$, TMSCl, crotonaldehyde, THF, –78°C; (ii) $Pr^iCH{=}PPh_3$, THF; (iii) (a) isobutyl phenyl sulfone, BuLi; PhCOCl, (b) Na/Hg, MeOH.



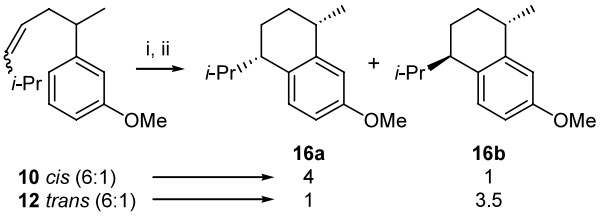
9 **13a** **14a**

Scheme 5. *Reagents and conditions*: (i) Py_2IBF_4, HBF_4, CH_2Cl_2, –78°C; (ii) Bu_3SnH, AIBN, toluene, 80°C.

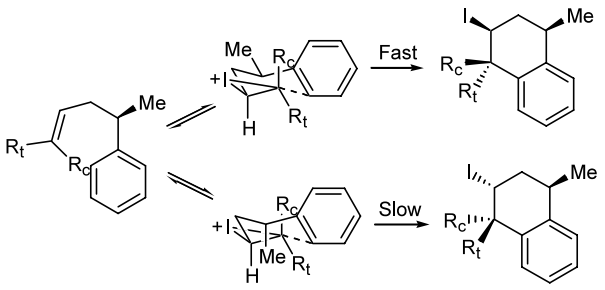


11 **13b** **14b**

Scheme 6. *Reagents and conditions*: (i) Py_2IBF_4, HBF_4, CH_2Cl_2, –78°C; (ii) Bu_3SnH, AIBN, toluene, 80°C.



Scheme 7. *Reagents and conditions*: (i) Py_2IBF_4, HBF_4, CH_2Cl_2, −78°C; (ii) Bu_3SnH, AIBN, toluene, 80°C.



Scheme 8.

requisite for future synthetic applications. Reductive deiodination of the crude mixture of diastereomers, under radical conditions,[14] furnished the sesquiterpene calamenene **14a** as a 3.5:1 mixture of *cis* and *trans* isomers in 40% overall yield. The spectroscopic data were identical to those reported for the natural products,[15] confirming the stereochemical outcome of the cationic cyclisation.

The analogous *trans* alkene **11** (ca. 6:1 *E*:*Z*) also underwent cationic cyclisation to give the iodotetralin **13b**,[16] together with a small amount of the diastereomer **13a**, but the yield was much poorer (Scheme 6). Substantial amounts of side products, including one which was tentatively identified as an iodo fluoro compound analogous to **8**, were also formed. Tin hydride reduction of the crude cyclisation product furnished calamenene **14b**, as a 6:1 *trans*:*cis* mixture, in 20% yield over the two steps. It is noteworthy that the geometrical isomers of the alkene gave different relative stereochemistry in the tetralins, and allowed us to prepare both *cis* and *trans* 1,4-disubstituted products selectively. This expeditious stereoselective synthesis of the calamenenes compares favourably with earlier syntheses,[1,17] and illustrates the potential of the alkene–arene cationic cyclisation strategy.

The methoxyarene **10** (ca. 1:6 *E*:*Z*) was prepared in order to determine if the cyclisation would tolerate the oxygen functionality required for the synthesis of pseudopterosins. Reaction with the I(I) reagent, followed by deiodination, furnished the cyclisation product **16a**[18] in 51% yield, as a 4:1 mixture of *cis* and *trans* isomers (Scheme 7). None of the regioisomer arising from cyclisation *ortho* to the methoxy group was observed. The results for the *trans* alkene **12** (ca. 6:1 *E*:*Z*) were similar, a 48% yield of tetralin **16b**,[19] as a 3.5:1 mixture of *trans* and *cis* isomers, being obtained. The NMR spectra of the iodotetralins and the tetralins were very similar to those of the calamenene analogues, so the relative stereochemistry can be assigned with confidence. The cyclisations of these methoxyarenes were much cleaner, and much less sensitive to variations in experimental conditions, than those of the less activated substrates **9** and **11**. It is clear that as the alkene becomes more hindered, greater activation of the arene is required. Use of PhSeCl, alone, and with AgOTf, failed to effect cyclisation of alkene **12**.

To account for the observed diastereoselectivity, we tentatively suggest that iodonium ion formation is reversible, and that cyclisation is faster for the diastereomers in which the benzylic methyl substituent is in a pseudoequatorial orientation, in the six-membered transition state (Scheme 8).

This method for preparing 1,4-disubstituted tetralins uses simple precursors and very mild conditions, and gives acceptable yields when the arene is activated. We have shown that diastereoselectivity can be obtained and that the relative stereochemistry can be controlled by changing the configuration of the alkene. The starting materials are obtained by a conjugate addition/alkylidenation sequence, which will provide easy access to a variety of substitution patterns, and to enantiopure materials. These results greatly increase our knowledge of the scope of iodonium ion-mediated arene alkene cyclisations, and they pave the way for the synthesis of various terpenes, including the pseudopterosins.

Acknowledgements

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11. **General I^+ cyclisation condition**: To a stirred solution of IPy_2BF_4 (1.110 g, 2.98 mmol, 1.3 equiv.) in dry CH_2Cl_2 (50 mL) at −78°C, under nitrogen was added dropwise 54% wt HBF_4–Et_2O (0.26 mL, 1.83 mmol, 0.8 equiv.) followed by a pre-cooled solution of the alkene **10** (500 mg, 2.29 mmol) in dry CH_2Cl_2 (2.3 mL). The temperature was kept at −78°C for 1 h and then the mixture was allowed to warm at −60°C (over 45 min). The reaction was quenched by adding dil. HCl-ice (∼15 mL), diluted with CH_2Cl_2 (∼15 mL) and washed with 5% $Na_2S_2O_3$ (2×15 mL) and saturated $NaHCO_3$ (∼15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude iodotetralin was stored under nitrogen in the dark, and was purified by column chromatography (SiO_2 gel, 40–60 petroleum ether).
12. NMR data for the cyclisation products, with assignments supported by COSY data, are shown below. Molecular mechanics calculations suggested a strong preference for a half-chair conformation in which the iodo and methyl groups were equatorial, and the isopropyl was pseudoaxial, presumably because of benzylic strain. The relative stereochemistry was assigned by analysis of the coupling constants for H-2 and H-4, which were fully consistent with the calculated values.
(1*RS*,2*SR*,4*RS*)-2-Iodo-1-isopropyl-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene 13a: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.68 (3H, d, J=6.7 Hz, CH_3 (^{i}Pr)), 1.15 (3H, d, J=6.7 Hz, CH_3 (^{i}Pr)), 1.31 (3H, d, J=6.7 Hz, 4-CH_3), 2.15 (1H, dt, J=14.1, 11.0 Hz, H-3), 2.27 (1H, m, $CH(Me)_2$), 2.31 (3H, s, $ArCH_3$), 2.57 (2H, m, H-3 and H-1), 2.99 (1H, br d quintet, J=11.0, 6.7 Hz, H-4), 4.78 (1H, ddd, J=4.4, 4.7, 11.4 Hz, H-2), 6.81 (1H, s, H-8), 7.02 (1H, d, J=8.1 Hz, ArH), 7.12 (1H, d, J=8.1 Hz, ArH).
(1*RS*,2*SR*,4*RS*)-2-Iodo-1-isopropyl-4-methyl-6-methoxy-1,2,3,4-tetrahydronaphthalene: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.71 (3H, d, J=6.8 Hz, CH_3 (^{i}Pr)), 1.12 (3H, d, J=6.8 Hz, CH_3 (^{i}Pr)), 1.32 (3H, d, J=6.8 Hz, 4-CH_3), 2.02–2.32 (2H, m, H-3 and $CH(Me)_2$), 2.51–2.64 (2H, m, H-3 and H-1), 3.00 (1H, apparent d quintet, J=10.6, 6.8 Hz, H-4), 3.80 (3H, s, OCH_3), 4.77 (1H, ddd, J=4.2, 4.9, 10.6 Hz, H-2), 6.71 (1H, dd, J=2.6, 8.2 Hz, H-7), 6.79 (1H, d, J=2.6 Hz, H-5), 6.95 (1H, d, J=8.2 Hz, H-8).
13. Diastereoselectivity of up to 6.6:1 has been observed in cyclisations using a selenium electrophile, see Ref. 5a.
14. **Radical reduction of the iodotetralins**. To a stirred solution of the iodotetrahydronaphthalene **13** (mostly **13a**) (372 mg, 1.08 mmol, 1 equiv.) in dry toluene (4 mL) and AIBN (9.0 mg, 0.05 mmol, 0.05 equiv.) was added (after freeze–thaw cycle) Bu_3SnH (0.4 mL, 1.4 mmol, 1.3 equiv.) under a constant flow of nitrogen. The reaction mixture was heated at 80°C for 4 h, and the toluene was evaporated. Purification by column chromatography (SiO_2 gel; petroleum ether:EtOAc, 98:2) afforded calamenene **14**, as a 3.5:1 mixture of *cis* and *trans* isomers, in 40% overall yield from the alkene **9**.
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16. NMR data for the cyclisation products, with assignments supported by COSY data, are shown below. Molecular mechanics calculations suggested that at least three substantial conformations were present. The observed coupling constants for H-2 were in good agreement with those predicted for the mixture of conformations, but the results were not unambiguous, because of the conformational complexity. Further strong support for the stereochemical assignment was obtained from NOESY experiments that showed, inter alia, strong correlations between H-2 and the isopropyl hydrogens, and between H-2 and H-4, thus confirming the 1,2-*trans* 2,4-*cis* stereochemistry.
(1*RS*,2*RS*,4*SR*)-2-Iodo-1-isopropyl-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene 13b: ^{1}H NMR (300 MHz, $CDCl_3$): 0.92 (3H, d, J=6.9 Hz, CH_3 (^{i}Pr)), 0.95 (3H, d, J=6.9 Hz, CH_3 (^{i}Pr)), 1.33 (3H, d, J=6.6 Hz, 4-CH_3), 2.01–2.09 (2H, m, H-3 and $CH(Me)_2$), 2.31 (3H, s, $ArCH_3$), 2.53–2.62 (2H, m, H-3 and H-1), 3.39 (1H, apparent t, J=5.2 Hz, H-4), 4.56–4.63 (1H, apparent dt, J=10.5, 5.3 Hz, H-2), 6.87 (1H, s, H-8), 7.01–7.14 (2H, m, ArH).
(1*RS*,2*RS*,4*SR*)-2-Iodo-1-isopropyl-4-methyl-6-methoxy-1,2,3,4-tetrahydronaphthalene: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (3H, d, J=7.0 Hz, CH_3 (^{i}Pr)), 0.97 (3H, d, J=6.7 Hz, CH_3 (^{i}Pr)), 1.36 (3H, d, J=7.0 Hz, 4-CH_3), 1.98–2.10 (2H, m, H-3 and $CH(Me)_2$), 2.58 (1H, ddd, J=4.6, 5.5, 13.3 Hz, H-3), 2.64–2.76 (1H, m, H-4), 3.37 (1H, apparent t, J=5.5 Hz, H-1), 3.82 (3H, s, OCH_3), 4.63 (1H, apparent dt, J=10.3, 5.2 Hz, H-2), 6.73 (1H, dd, J=2.6, 8.4 Hz, H-6), 6.81 (1H, d, 2.6 Hz, H-5), 7.00 (1H, d, J=8.4 Hz, H-8). ^{13}C NMR ($CDCl_3$ 125 MHz) δ: 19.76; 20.13; 20.67; 28.49; 33.91; 34.80; 45.72; 55.41; 57.19; 110.83; 111.32; 130.24; 130.50; 143.13; 158.29.
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18. ***cis*-1-Isopropyl-4-methyl-6-methoxy-1,2,3,4-tetra-hydronaphthalene 16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.76 (3H, d, J=6.7 Hz), 1.02 (3H, d, J=6.9 Hz), 1.27 (3H, d, J=7.1 Hz), 1.56–1.86 (4H, m), 2.14–2.28 (1H, m), 2.58 (1H, apparent q, J=6.2 Hz), 2.80–2.92 (1H, m), 3.78 (3H, s), 6.68–6.71 (1H, m), 7.12 (d, 1H, 9.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 17.72, 19.94, 21.59, 22.56, 23.50, 28.88, 31.34, 33.43, 43.29, 111.56, 113.56, 129.33, 132.36, 144.44, 157.50.
19. ***trans*-1-Isopropyl-4-methyl-6-methoxy-1,2,3,4-tetra-hydronaphthalene 16b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.74 (3H, d, J=6.8 Hz), 1.01 (3H, d, J=6.8 Hz), 1.30 (3H, d, J=6.8 Hz), 1.34–1.44 (1H, m), 1.56–1.70 (1H, m), 1.81–1.89 (1H, m), 1.95–2.02 (1H, m), 2.66–2.72 (1H, m), 2.80 (1H, apparent sextet, J=7.0 Hz), 3.81 (3H, s), 6.72 (1H, dd, J=2.7, 8.5 Hz) 6.80 (1H, dd, J=0.8, 2.7 Hz), 7.14 (1H, d, J=8.5 Hz). ^{13}C NMR ($CDCl_3$ 125 MHz) δ: 17.61; 21.44; 21.84; 22.52; 30.90; 32.08; 33.35; 43.50; 55.35; 111.11; 112.54; 129.23; 132.54; 144.56; 157.52.