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Asymmetric Synthesis of 2-Aryl-Tetrahydropyrans *via* Arene Chromium Tricarbonyl Methodology 2: 2-Aryl-3-Ethyl-4-Chloro-Tetrahydropyrans

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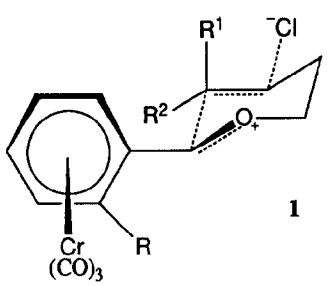
Abstract: Treatment of acetals derived from *o*-tolualdehyde chromium tricarbonyl and *o*-anisaldehyde chromium tricarbonyl with Z- and E-hex-3-en-1-ol and titanium tetrachloride generated, after decomplexation, completely stereoselectively the corresponding *r*-2-*o*-aryl-*c*-3-ethyl-*c*-4-chloro-tetrahydropyrans and *r*-2-*o*-aryl-*t*-3-ethyl-*c*-4-chloro-tetrahydropyrans respectively. This methodology was applied to the asymmetric synthesis of homochiral (R,R,S)- and (S,R,R)-2-*o*-anisyl-3-ethyl-4-chloro-tetrahydropyran from homochiral *o*-anisaldehyde chromium tricarbonyl and Z- and E-hex-3-en-1-ol respectively.

In the preceding paper[1] we demonstrated that treatment of acetals derived from *ortho* substituted benzaldehyde chromium tricarbonyl complexes and methanol with homoallylic alcohol and titanium tetrachloride produced the corresponding (RS,RS,SR)-*cis*-2-aryl-4-chloro-tetrahydropyran complexes completely diastereoselectively to yield, after decomplexation, *cis*-2-aryl-4-chloro-tetrahydropyrans.

The proposed mechanism involved intramolecular cyclisation of an intermediate O-homoallylic oxonium ion **1** (R^1,R^2 = H) in a conformation with the benzylic hydrogen *syn* to the *ortho* substituent: The relative stereochemistry between the arene chromium tricarbonyl moiety and C2 being set by addition to the least hindered face of the oxonium ion away from the chromium tricarbonyl, while that between C2 and C4 was considered to be derived from a chair transition state with the arene chromium tricarbonyl adopting an equatorial position and with antiperiplanar addition of the oxonium and chloride ions across the double bond.



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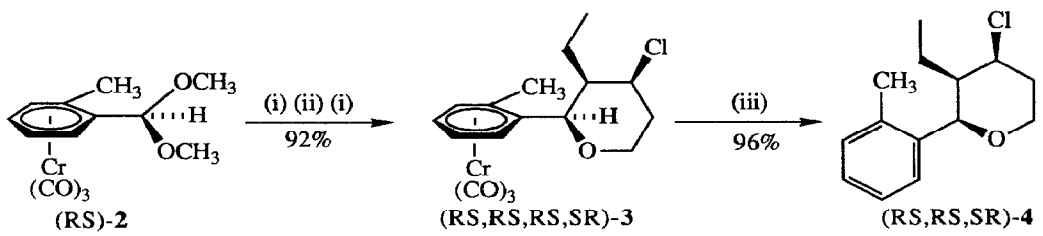
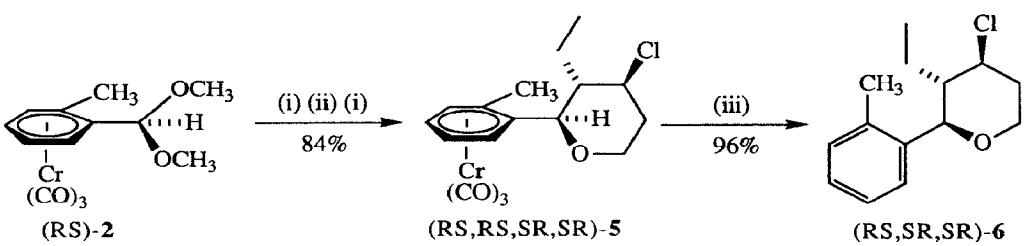
If the above analysis is correct, introduction of a substituent onto the terminal position of the double bond of the homoallylic alcohol should allow the stereospecific introduction[2] of this substituent into the 3-position of the tetrahydropyran product. For a *cis*-δ-substituted homoallylic alcohol the substituent should be axial in the transition state (**1**, R^2 = H), while for a *trans*-δ-substituted homoallylic alcohol the substituent should lie equatorial. The former case should give rise, therefore, to *all-cis*-2,3,4-trisubstituted tetrahydropyrans. We describe herein the validation of this prediction using Z- and E-hex-3-en-1-ol and acetals derived from methanol and both *o*-tolualdehyde chromium tricarbonyl and *o*-anisaldehyde chromium tricarbonyl.[3]

Treatment of the racemic acetal complex (RS)-**2**, at -78°C with titanium tetrachloride (0.5 equivalents), Z-hex-3-en-1-ol (3 equivalents) and titanium tetrachloride (1.5 equivalents) generated, as predicted, the complex (RS,RS,RS,SR)-**3**[4] as a single diastereoisomer by ^{1}H nmr spectroscopy (Scheme 1). The expected *all-cis* relationship of the three substituents on the tetrahydropyran ring was confirmed, and the stereochemistry of the *o*-tolyl chromium tricarbonyl moiety relative to C2, C3 and C4 was unambiguously established as (RS,RS,RS,SR) by a single crystal X-ray structure analysis of **3**.[5] Decomplexation of **3** gave *r*-2-*o*-tolyl-*c*-3-ethyl-*c*-4-chloro-tetrahydropyran (RS,RS,SR)-**4** (Scheme 1).The axial positions of the C2-H, and C4-H together with the equatorial position of the C3-H followed from analysis of the ^{1}H nmr coupling constant data.[6]



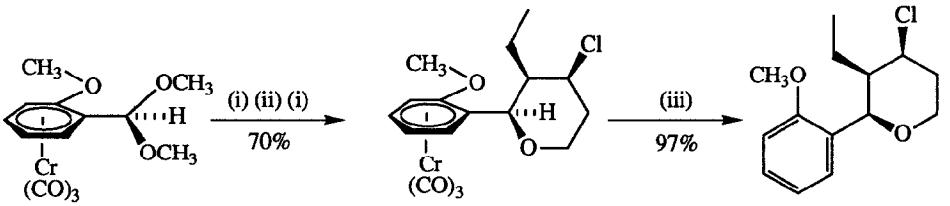
Scheme 1: Reagents: (i) $TiCl_4$, -78°C; (ii) Z-CH_3CH_2CH=$CHCH_2CH_2OH$, (iii) O_2

Treatment of the racemic acetal complex (RS)-**2** and E-hex-3-en-1-ol, as above, generated the complex (RS,RS,SR,SR)-**5** completely stereoselectively (Scheme 2). That all three tetrahydropyran substituents were equatorial was established from the ^{1}H nmr coupling constant data,[7] while the relative stereochemistry of the *o*-tolyl chromium tricarbonyl moiety was assigned by analogy with the formation of **3**. Decomplexation of **5** gave diastereoisomerically pure racemic *r*-2-*o*-tolyl-*t*-3-ethyl-*c*-4-chloro-tetrahydropyran (RS,SR,SR)-**6**.



Scheme 2: Reagents: (i) $TiCl_4$, -78°C; (ii) E-CH_3CH_2CH=$CHCH_2CH_2OH$, (iii) O_2

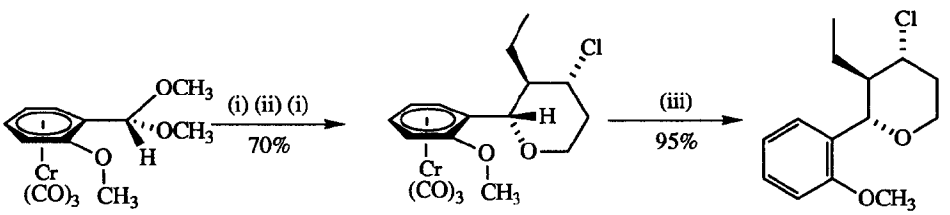
The Lewis acid promoted cyclisations described above for the *o*-tolyl chromium tricarbonyl complexes were also completely stereoselective for the *o*-anisyl derivatives. Thus, starting from homochiral (R)-(+)-**7**, treatment with titanium tetrachloride and Z-hex-3-en-1-ol generated (R,R,R,S)-(+)-**8** as a single diastereoisomer $[\alpha]_D^{22}$+186 (c = 0.007, $CHCl_3$). Decomplexation of **8** gave homochiral *r*-2-*o*-anisyl-*c*-3-ethyl-*c*-4-chloro-tetrahydropyran (R,R,S)-**9**, the relative stereochemistry within **9** being assigned as before.[8] Complex (R,R,S)-**9** $[\alpha]_D^{22}$+107.3 (c = 0.06, $CHCl_3$) was judged homochiral (>98 % ee) by analysis of its ^1H nmr spectrum in the presence of (S)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, since only one enantiomer could be detected in comparison with the racemate. The absolute configuration of (R,R,S)-**9** follows from the known absolute configuration of (R)-(+)-**7**.[1,9]



(R)-(+)-**7** (R,R,R,S)-(+)-**8** (R,R,S)-(+)-**9**

Scheme 3: Reagents: (i) $TiCl_4$, -78°C; (ii) Z-CH_3CH_2CH=$CHCH_2CH_2OH$; (iii) O_2, Et_2O, hυ

Starting from (S)-(-)-**7** and E-hex-3-en-1-ol, the above reaction conditions resulted in the completely stereoselective formation of the complex (S,S,R,R)-**10**, $[\alpha]_D^{22}$ -93.3 (c = 0.21, $CHCl_3$), and, after decomplexation, homochiral *r*-2-*o*-anisyl-*t*-3-ethyl-*c*-4-chloro-tetrahydropyran (S,R,R)-**11** $[\alpha]_D^{22}$ -87.0 (c = 0.12, $CHCl_3$), (Scheme 4). The relative and absolute configurations of (S,S,R,R)-**10** and (S,R,R)-**11** were assigned as before.[10]

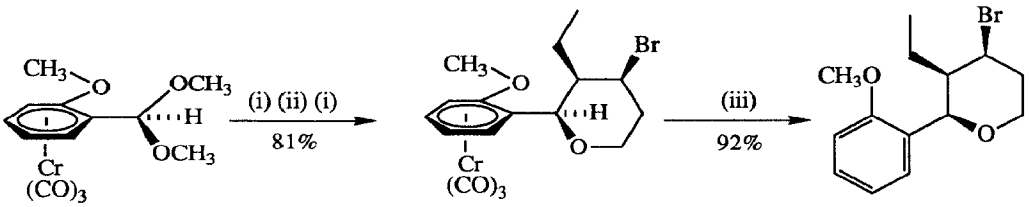


(S)-(-)-**7** (S,S,R,R)-(-)-**10** (S,R,R)-(-)-**11**

Scheme 4: Reagents: (i) $TiCl_4$, -78°C; (ii) E-CH_3CH_2CH=$CHCH_2CH_2OH$; (iii) O_2, Et_2O, hυ

Extension of this methodology to include the synthesis of 2-aryl-3-alkyl-4-bromo-tetrahydropyrans was accomplished by using tin tetrabromide as the Lewis acid. Thus, treatment of racemic acetal (RS)-**7** with two portions of tin tetrabromide and Z-hex-3-en-1-ol, as indicated in Scheme 5, generated complex **12** and then, after decomplexation, free arene **13**, in 75% overall yield from **7**. Analysis of the crude ^1H nmr spectrum of the product **12** indicated the completely selective nature of the cyclisation and also allowed us to assign the complex

13 as being the *all-cis* isomer.[11] The stereochemical outcome of this reaction can be rationalised by invoking a mechanism analogous to that described above for the titanium tetrachloride promoted cyclisations.



(RS)-7 (RS,RS,RS,SR)-**12** (RS,RS,SR)-**13**

Scheme 5: Reagents: (i) $SnBr_4$, -78°C; (ii) Z-$CH_3CH_2CH{=}CHCH_2CH_2OH$; (iii) O_2, EtO_2, hυ

In conclusion, we have demonstrated the potential of arene chromium tricarbonyl methodology for the asymmetric synthesis of diastereoisomerically pure 2-aryl-3-alkyl-4-chloro-tetrahydropyrans and provided further justification for the mechanistic model previously proposed for this type of cyclisation.[1]

Acknowledgement:
We thank ICI Pharmaceuticals (Macclesfield) and the SERC for a CASE award (to T.J.D.).

References and notes:

1. S. G. Davies, T. J. Donohoe and M. A. Lister, see preceding paper.
2. L. E. Overmann, A. Castaneda and T. A. Blumenkopf, *J. Amer. Chem. Soc.*, 1986, **108**, 1303.
3. S. G. Davies, R. F. Newton and J. M. J.Williams, *Tetrahedron Lett .*, 1989, **22**, 2967.
4. For a description of the application of the Cahn-Ingold-Prelog notation of absolute stereochemistry within molecules possessing planar chirality, such as arene chromium tricarbonyl complexes, see K. Schlogl, *Topics in Stereochem.*, 1967, **1**, 39. For the purposes of this paper, the aldehyde, acetal or tetrahydropyranyl substituent is assumed to be attached to the 1-position of the arene. The absolute stereochemistry of the arene chromium tricarbonyl fragment is specified at this centre regardless of the other ring substituent. In all cases the configuration of the arene chromium tricarbonyl moiety is specified first followed by the others in the usual way.
5. S. G. Davies, T. J. Donohoe and A. J. Edwards, unpublished results.
6. All new compounds have been fully characterised. Selected ^{1}H nmr for **4**, δ 4.61 (d, 1H, J= 1.4, ArCHOCH$_2$), 4.41 (dt, 1H, J= 11.8, 5.1, CHCl).
7. Selected ^{1}H nmr for **5**, δ 3.98 (dt, 1H, J= 4.3, 10.3, CHCl), 3.96 (d, 1H, J= 10.2, ArCHOCH$_2$).
8. Selected ^{1}H nmr for **9**, δ 4.4 (d, 1H, J=1.4, ArCHOCH$_2$), 4.36 (dt, 1H, J=10.9, 4.4, CHCl).
9. L. A. Bromley, S. G. Davies and C. L. Goodfellow, *Tetrahedron Asymmetry*, 1991, **2**, 139.
10. Selected ^{1}H nmr data for **10**, δ 4.2 (d, 1H, J=9.3, ArCHOCH$_2$), 4.0 (dt, 1H, J= 4.3, 12.7, CHCl).
11. Selected ^{1}H nmr data for **13**, δ 4.8 (s, 1H, ArCHOCH$_2$), 4,6 (dt, 1H, J=12.7, 4.3, CHBr).