A Short Olefin Metathesis-Based Route to Enantiomerically Pure Arylated Dihydropyrans and α,β-Unsaturated δ-Valero Lactones

Holger Wildemann,† Pascal Dünnelkmann,‡ Michael Müller,‡ and Bernd Schmidt*,†

FB Chemie der Universität Dortmund, Organische Chemie, D-44221 Dortmund, Germany, and Institut für Biotechnologie 2, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany

bschmidt@chemie.uni-dortmund.de

Received September 25, 2002

The synthesis of arylated dihydropyrans and unsaturated lactones starting from enantiomerically pure α-hydroxy ketones (prepared by an enzyme-catalyzed benzoin condensation) is described. The key steps are a highly diastereoselective addition of vinyl metal compounds under chelate control and a ruthenium-catalyzed ring-closing olefin metathesis reaction. Elucidation of the relative configuration of the final products was achieved by NOE experiments.

Arylated heterocycles have been a synthetic target in several pharmaceutical research laboratories. Potential applications range from 5-Lipoxygenase inhibitors1 to NK-1 receptor antagonists2,3 and ligands for receptors of neurotransmitters.4,5 Methods for the introduction of aryl moieties to heterocycles include Heck reactions6 or Stille couplings,7 asymmetric Michael reactions of aryl acetic acids,6 and addition of aryl metal compounds to heterocycloalkanes.8 Two examples of biologically active heterocycles synthesized by this method are depicted in Figure 1: the piperidine 1 shows adrenoceptor agonist activity,7 while the tetrahydropyran 2 inhibits leukotriene synthesis in vitro.9

The structural pattern present in 2 inspired a short and highly diastereoselective synthesis of more densely functionalized enantiomerically pure analogues. Our synthetic concept is based on the ring-closing olefin metathesis reaction10–12 and uses enantiomerically pure α-hydroxy-aryl ketones 3 as starting materials. The ketones 3 were obtained on a preparative scale in high chemical and optical yield by benzaldehyde lyase (BAL)-catalyzed benzoin condensation-like reaction from aromatic aldehydes and acetaldehyde.12,13 Using this thiamine diphosphate (ThDP)-dependent enzyme in an aqueous buffer solution a large number of highly enantio-enriched (R)-benzoins and (R)-2-hydroxy-1-phenyl-1-propanones substituted in ortho-, meta-, and para-positions by diverse moieties are available in one reaction step. Additionally, direct access to the corresponding (S)-enantiomers is also given by using the same enzymes’ racemic resolution ability or by using other ThDP-dependent enzymes.14,15

Following the sequence outlined in Scheme 1, dihydropyrans 7a–e were obtained as single diastereomers in enantiomerically pure form.

Starting from α-hydroxy ketones 3, allyloxy ketones 4 were obtained using silver oxide and allyl bromide.16 By using this method, racemization at the α-carbon was avoided and allyl ethers 4 were obtained in an enantio-
modified stationary phases. The amount of the benzoin and compared with material obtained via the racemization. Racemic proved that the vinylation reaction occurs without any tiomer was below the detection limit corresponding to an of the dienes catalyst \((\text{in the presence of 3 mol }\% \text{ of the first generation Grubbs' temperature, the dienes }^6\text{)}\)

\[ A \rightarrow B \text{ 6. First (A) and second (B) generation Grubbs' catalyst.} \]

become higher in energy compared to derivatives not substituted in the ortho-position.

Modification of the sequence outlined above allows the conversion of \(\alpha\)-hydroxy ketones to \(\alpha,\beta\)-unsaturated lactones \(10\). Starting from \(3c, f\), vinylation to the corresponding diol \(8c, f\) is achieved by addition of excess vinylmagnesium chloride. Again, HPLC on chirally modified stationary phases proved that no racemization occurs on this step. For this purpose, racemic \(8c\) was prepared from the corresponding racemic benzoin and compared with material obtained from enantiomerically pure \((R)\)-

\[ 3c \]

\[ \text{TABLE 1. Synthesis of Arylated Dihydropyrans} \]

| compd | R<sup>1</sup> | R<sup>2</sup> | % yield of 4 | % yield of 6 (dr) | % yield of 7 |
|-------|-------------|-------------|--------------|------------------|--------------|
| \((R)\)-3a | Ph | Ph | 90 | 10:1 | 99 (<19:1) | 90 |
| \((R)\)-3b | Me | Ph | 47 | 1:1 | 67 (<19:1) | 86 |
| \((S)\)-3b | Me | Ph | 47 | 1:1 | 62 (<19:1) | 80 |
| \((R)\)-3c | 3-OMePh | 3-OMePh | 99 | >19:1 | 79 (<19:1) | 90 |
| \((R)\)-3d | 2-Cl-Ph | 2-Cl-Ph | 75 | 5:1 | 85 (<19:1) | 75 |
| \((R)\)-3e | 4-Br-Ph | 4-Br-Ph | 73 | 5:1 | 90 (<19:1) | 78 |

merically pure form. If strong bases, such as NaH, are used, an O-allylation-Wittig rearrangement takes place, leading to aryl-allyl carbamions.\(^{17}\). In the case of \((R)\)- and \((S)\)-3b, allyl benzoate was formed as an inseparable byproduct. Obviously, oxidative cleavage of the acyloin linkage occurs, leading to benzoic acid, which is then allylated to give the corresponding allyl ester. In all other cases, only minor amounts of allyl esters 5 result. The amount of 5 increases with an increasing amount of silver oxide, thus, a large excess of silver oxide should be carefully avoided. By treatment of the \(\alpha\)-allyloxy ketones 4 with vinylmagnesium chloride in THF/ether at low temperature, the dienes 6 were obtained with very high diastereoselectivity. In all cases investigated, only one diastereomer could be detected in the proton NMR spectrum of the crude reaction mixture, corresponding to a diastereomeric ratio higher than 19:1. For 6a we proved that the vinylation reaction occurs without any racemization. Racemic 6a was prepared from commercial benzoin and compared with material obtained via the same sequence from \((R)\)-3a using HPLC on chirally modified stationary phases. The amount of the \(S\)-enantiomer was below the detection limit corresponding to an enantiomeric excess of >99%. Ring-closing metathesis of the dienes 6 to the dihydropyrans 7 proceeded smoothly in the presence of 3 mol % of the first generation Grubbs' catalyst (A in Figure 2). Only 6d required 10 mol % of the ruthenium catalyst for complete conversion to the dihydropyrans 7d. The significantly reduced reactivity of 6d might be explained by steric interactions of the substituent in the ortho-position of the aromatic ring with the ligand sphere of the ruthenium complex. As a consequence, conformations suitable for ring closure

\[ \text{FIGURE 2.} \]

\[ A \rightleftharpoons B \text{ 7a, b, e and the lactone 10f. For the dihydropyrans a NOE interaction of H2 with one of the protons H6 is indicative of a pseudoxial} \]

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**SCHEME 2**

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R^2

R^1

3c,f

R^2

R^1

10c,f
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| 3  | R^1 | R^2     | % yield of 8 (dr) | % yield of 9 | % yield of 10 |
|----|-----|---------|-------------------|--------------|---------------|
| (R)-3c | 3-OCH_3-Ph | 3-OCH_3-Ph | 76 (17:1)        | 80           | 95            |
| (R)-3f | -CH_3    | 3-Cl-Ph  | 81 (~19:1)       | 72           | 90            |

**TABLE 2. Synthesis of Arylated Lactones**

**FIGURE 3.** Representative NOE interactions in 7e and 10f.

orientation of these protons. H2 shows an NOE to the ortho-protons of the aromatic ring in the 3-position and to the substituent in the 2-position. However, no NOE interaction to the OH proton was observed. In contrast, the OH proton shows NOEs to both aromatic substituents and to the olefinic proton H4, but not to H2. From these observations we conclude that the substituents at C2 and C3 are trans-arranged. These NOE interactions are summarized for the example 7e in Figure 3. For the lactone series, NOEs were recorded for 10f. Indicative NOE interactions are found between H2 and both ortho protons of the aryl moiety. NOE interactions between the methyl group in the 2-position and these ortho protons are significantly weaker (Figure 3).

The relative R5-stereochemistry of the alcohols 6 and 8 and the high degree of diastereoselectivity originates from a chelation effect first proposed by Cram ("Cram's cyclic model")24,25. The oxygen of the α-allyloxy substituent or the hydroxy group and the carbonyl oxygen form a five-membered chelate complex, which is preferentially attacked from the sterically less shielded side, as outlined for the formation of 6a in Figure 4. The addition of organomagnesium compounds to α-hydroxy ketones and factors governing the stereoselectivity of the addition step have already been thoroughly investigated.25,26

In conclusion, we have developed a highly diastereoselective route to enantiomerically pure dihydropyrans and α,β-unsaturated lactones bearing one or two aromatic substituents. The synthetic concept is based on the use of α-hydroxy ketones which are conveniently obtained in enantiomerically pure form, a highly diastereoselective vinylation relying on efficient chelate control, and a ring-closing olefin metathesis step.

**Experimental Section**

**General.** All experiments were conducted in dry reaction vessels in an atmosphere of dry argon. Solvents were purified by standard procedures. 1H NMR spectra were recorded at 400 or 500 MHz in CDCl_3 with CHCl_3 (δ 7.24 ppm) as internal standard. Coupling constants are given in hertz. 13C NMR spectra were recorded at 100 or 125 MHz in CDCl_3 with CDCl_3 (δ 77.0 ppm) as internal standard. The number of coupled protons was analyzed by DEPT or APT experiments and is denoted in parentheses following the δ_C values. Signal assignment for cyclic products follows a numbering scheme where the oxygen atom is numbered as 1 and the α-carbon atom bearing the substituent R^1 (cf. Schemes 1 and 2) as C2. Selective 1D-NOE experiments were conducted using shaped pulses and pulsed field gradients at 600 MHz with a mixing time of 800 ms. IR spectra were recorded as films on NaCl or KBr plates or as KBr disks. The peak intensities are defined as strong (s), medium (m), and weak (w). Mass spectra were obtained at 70 eV. Optical purities were determined by HPLC using a HP-LC-1050 system equipped with a Daicel Chiralcel OD, a Daicel Chiralcel OD-H, or a Daicel Chiralpak AD column. Starting materials 3 were employed with ee values >99%, except for (S)-3b (ee 92%) and (R)-3d (ee 97%). The ruthenium catalyst A^27 was purchased from Fluka, the second generation catalyst B was prepared following a literature procedure.28

**General Procedure for the Preparation of Allyloxy Ketones 4.** To a solution of the corresponding α-hydroxy ketone 3 (2.0 mmol) and allyl bromide (0.26 mL, 3.0 mmol) in ether (30 mL) was added silver oxide (700 mg, 3.0 mmol). The mixture was heated to reflux for 2 h, and stirring was continued at ambient temperature in the dark for 2 days. All solids were removed by filtration through a small pad of Celite.

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the solvent was removed in vacuo, and the residue was purified by flash chromatography on silica using cyclohexane/MTBE mixtures as eluents.

(R)-2-Allyloxy-1,2-diphenylethanone (4a). Starting from (R)-benzoin (3a) (700 mg, 3.3 mmol), 4a (750 mg, 90%) was obtained. Anal. Calcld for C24H22O2: C, 80.39; H, 6.39. Found: C, 80.75; H, 6.25. MS (EI): m/z 253 (M+ + 1), 10.10, 105 (100). IR (film): 1694 (s) cm⁻¹, 1H NMR (400 MHz, CDCl3): δ 7.94–7.90 (2H), 7.44–7.38 (3H), 7.33–7.18 (5H), 5.88 (dddd, 1H, J = 17.3, 10.3, 5.5, 5.5), 5.60 (s, 1H), 5.23 (dddd, 1H, J = 17.3, 1.5, 1.5, 1.5), 5.15 (dddd, 1H, J = 10.3, 1.5, 1.5, 1.5), 4.04 (ddm, 2H, J = 1.5). 13C NMR (100 MHz, CDCl3): δ 197.3 (0), 136.2 (0), 135.0 (0), 134.0 (1), 133.2 (1), 129.1 (1), 128.8 (1), 128.4 (1), 125.6 (1), 124.1 (1), 118.1 (2), 83.9 (1), 70.5 (2). (α)D20 + 36.4 (c 1.0, CH2Cl2).

(S)- and (R)-2-Allyloxy-1-phenylpropan-1-one ((S)-4b and (R)-4b). Starting from either enantiomer of 3b (490 mg, 3.3 mmol), the corresponding enantiomer of 4b (approximately 290 mg, 47%) and benzoic acid allyl ester were obtained as an inseparable mixture, which was used for subsequent transformations. The yield of 4b was estimated from the NMR spectrum of the mixture. NMR spectroscopic data for 4b (obtained from the mixture): 1H NMR (400 MHz, CDCl3): δ 7.94–7.90 (2H), 7.45 (s, 1H), 7.39–7.31 (2H), 5.81 (dddd, 1H, J = 17.3, 10.3, 5.5, 5.5), 5.17 (dddd, 1H, J = 17.3, 1.5, 1.5, 1.5), 5.08 (ddm, 1H, J = 10.3), 4.67 (q, 1H, J = 7.0), 4.00 (ddm, 1H, J = 12.5, 5.5), 3.85 (ddm, 1H, J = 12.5, 5.8), 1.41 (d, 3H, J = 7.0). 13C NMR (100 MHz, CDCl3): δ 200.5 (0), 134.1 (0), 133.2 (1), 128.6 (1), 128.5 (1), 128.5 (1), 117.5 (2), 77.9 (1), 70.5 (2), 18.7 (3).

(R)-2-Allyloxy-1,2-bis-(3-methoxyphenyl)ethanone (4c). Starting from 3c (565 mg, 2.1 mmol), 4c (640 mg, 99%) was obtained.

(R)-2-Allyloxy-1,2-bis-(2-chlorophenyl)ethanone (4d). Starting from 3d (420 mg, 1.5 mmol), 4d (361 mg, 75%) was obtained after purification by column chromatography on silica.

(R)-2-Allyloxy-1,2-bis-(4-bromophenyl)ethanone (4e). Starting from 3e (580 mg, 1.5 mmol), 4e (450 mg, 73%) was obtained after purification by column chromatography on silica.

General Procedure for the Preparation of Vinyl Carbinols 6. A solution of the corresponding ketone 4 (4.0 mmol) in ether (100 mL) was cooled to −78 °C. A solution of tin(II) chloride in THF (1.7 M, 4.7 mL, 7.9 mmol) was added, and the mixture was stirred until the starting material was completely consumed, as indicated by TLC. The mixture was poured onto aqueous NH4Cl solution, the organic layer was separated, and the aqueous layer was extracted with MTBE. The combined organic extracts were dried with MgSO4, filtered, and evaporated. The residue was purified by flash chromatography on silica.

(1R,2S)-1-Allyloxy-1,2-diphenylbut-3-en-2-ol (6a). Starting from 4a (0.70 g, 2.8 mmol), 6a (0.77 g, 99%) was obtained. Analogously, from (1R,2S)-4-(a-allyloxy-(3S)-3-phenylpropan-2-yl)pentan-1-ol (6b). Starting from (R)-4b (290 mg, 1.5 mmol of a mixture with 1-allyl benzoxane), (3S,4R)-6b (200 mg, 67%) was obtained. Analogously, from (S)-4b (270 mg, 1.4 mmol), (3R,4S)-6b (190 mg, 62%) was obtained. In both cases the products were contaminated with allylbenzoate from the preceding step. MS (EI): m/z 191 (M+ – CH3, 100), 105 (85). 1H NMR (400 MHz, CDCl3): δ 7.44–7.40 (2H), 7.33–7.28 (2H), 7.21 (1H, J = 10.0, 10.8), 7.10 (2H), 7.01 (2H, J = 10.0, 10.0). 13C NMR (100 MHz, CDCl3): δ 142.7 (0), 141.5 (1) 136.6 (0), 134.3 (1), 128.7 (1), 127.8 (1), 127.5 (1), 127.5 (1), 126.8 (1), 126.2 (1), 117.0 (2), 114.4 (2), 86.8 (1), 78.5 (5), 70.0 (2). (α)D20 = +86 (c 1.00, CH2Cl2).
Acrylic Acid (IR,2S)-2-(3-Chlorophenyl)-2-hydroxy-1-methylbut-3-enyl Ester (9f). Starting from 8f (240 mg, 1.1 mmol), 9f (210 mg, 72%) was obtained. Anal. Calcld for C₂H₇O₂Cl: C, 63.04; H, 5.67. Found: C, 63.05; H, 5.45. MS (EI, 70 eV): m/z 194 (5%, M⁻ + HCl), 167 (40), 55 (100). IR (film) 3491 (s), 1713 (s), 1635 (m), 1617 (m), 808 (m), 786 (m), 697 (m) cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.51 (s, 1H), 7.34 (d, 1H, J = 7.7), 7.29 (d, 1H, J = 7.7), 7.25 (dd, 1H, J = 7.7, 7.7), 6.41 (d, 1H, J = 17.2), 6.22 (dd, 1H, J = 17.0, 10.7), 6.11 (dd, 1H, J = 17.2, 10.5), 5.86 (d, 1H, J = 10.5), 5.41 (q, 1H, J = 6.2), 5.36 (d, 1H, J = 17.2), 5.21 (d, 1H, J = 10.7), 2.40 (s, 1H), 1.08 (d, 3H, J = 6.2). ¹³C NMR (125 MHz, CDCl₃): δ 163.5 (3), 144.0 (1), 141.3 (4), 133.4 (0), 131.3 (2), 129.6 (1), 128.2 (1), 127.4 (1), 125.8 (1), 123.6 (1), 114.6 (2), 78.1 (0), 74.9 (1), 14.0 (3). [a]D²¹ = -24.5 (c 0.40, CHCl₃).

General Procedure for the Ring Closing Metathesis of Acrylates 9. To a solution of the corresponding acrylate 9 (0.6 mmol) in toluene (30 mL) was added ruthenium complex B (19 mg, 0.4 mol%). The solution was heated to 70 °C until the starting material was completely consumed (approximately 1 h). The solvent was evaporated and the residue was purified by flash chromatography on silica to give the corresponding lactone 10.

Acrylic Acid (IR,2S)-2-Hydroxy-1,2-bis(3-methoxyphenyl)but-3-enyl Ester (9c). Starting from 8c (130 mg, 0.4 mmol). 10c (115 mg, 95%) was obtained as colorless crystals, mp 120 °C. Signal assignments in the H NMR spectrum are based on H-COSY, and signal assignments in the C NMR spectrum are based on C–H correlation spectroscopy. Anal. Calcld for C₂₁H₂₂O₅: C, 71.17; H, 6.26. Found: C, 71.20; H, 6.25. MS (EI, 70 eV): m/z 326 (M⁻ + HCl), 190 (100). IR (film) 3376 (s), 1721 (s), 1604 (s), 797 (s), 779 (s) cm⁻¹. ¹H NMR (600 MHz, CDCl₃): δ 7.73 (dd, 1H, J = 8.0, 8.0, C3-Ar-H5), 7.06 (dd, 1H, J = 8.0, 8.0, C2-Ar-H5), 6.98 (d, 1H, J = 9.9, H4), 6.83 (dd, 1H, J = 8.4, 2.2, C3-Ar-H4), 6.79 (dd, 1H, J = 8.1, 2.2, C2-Ar-H4), 6.74 (d, 1H, J = 7.7, C3-Ar-H6), 6.66 (s, 1H, C3-Ar-H2), 6.52 (s, 1H, C2-Ar-H2), 6.48 (d, 1H, J = 7.7, C2-Ar-H6), 6.28 (d, 1H, J = 9.8, H5), 5.54 (s, 1H, H2), 3.67 (s, 3H, C3-Ar-OC), 3.59 (s, 3H, C2-Ar-OC), 2.94 (s, 1H, OH). ¹³C NMR (125 MHz, CDCl₃): δ 136.8 (0), 159.6 (0), 159.6 (0), 139.8 (0), 128.8 (1), 128.5 (1), 120.1 (1), 118.5 (1), 115.4 (2), 113.9 (1), 113.0 (1), 112.8 (1), 111.9 (1), 79.7 (1), 79.2 (0), 55.2 (5), 55.1 (3). [a]D²¹ = -24.5 (c 0.40, CHCl₃).

Acknowledgment. This work was generously supported by the Deutsche Forschungsgemeinschaft (P.D., M.M.: SFB 380) and the Fonds der Chemischen Industri.
trie. Financial support by the Department of Chemistry, Universität Dortmund, is also gratefully acknowledged. B.S. thanks Dr. B. Plietker for HPLC measurements and Dr. B. Costisella for conducting nonroutine NMR experiments.

Supporting Information Available: Copies of $^1$H and $^{13}$C NMR spectra of 4c–e, 6d,e, 7c–e, and 8c; analytical data for compounds 4c–e, 6c–e, and 7c–e. This material is available free of charge via the Internet at http://pubs.acs.org.

J 00264729