Practical Preparation of Both Optically Pure Enantiomers of But-1-yn-3-ol, Oct-1-yn-3-ol and 6-Methylhept-2-yn-4-ol Using Biocartol as Resolving Agent

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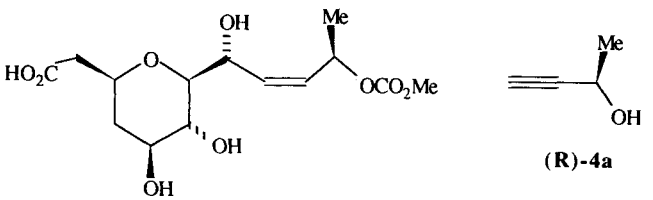
Received 4 July 1994

A new facile preparation of optically pure secondary alkynols has been developed. This involves resolution of the corresponding racemic alcohols using biocartol as the resolving agent.

In connection with our studies towards the synthesis of biologically active cyclopropanes[1] such as ambruticine,[2] we confronted the problem of producing the compound shown in Scheme 1 in optically pure form. Owing to the difficulty of obtaining this material starting from the optically pure (*R*)-but-1-yn-3-ol [(*R*)-**4a**], it became desirable to develop a practical preparation of (*R*)-**4a**.



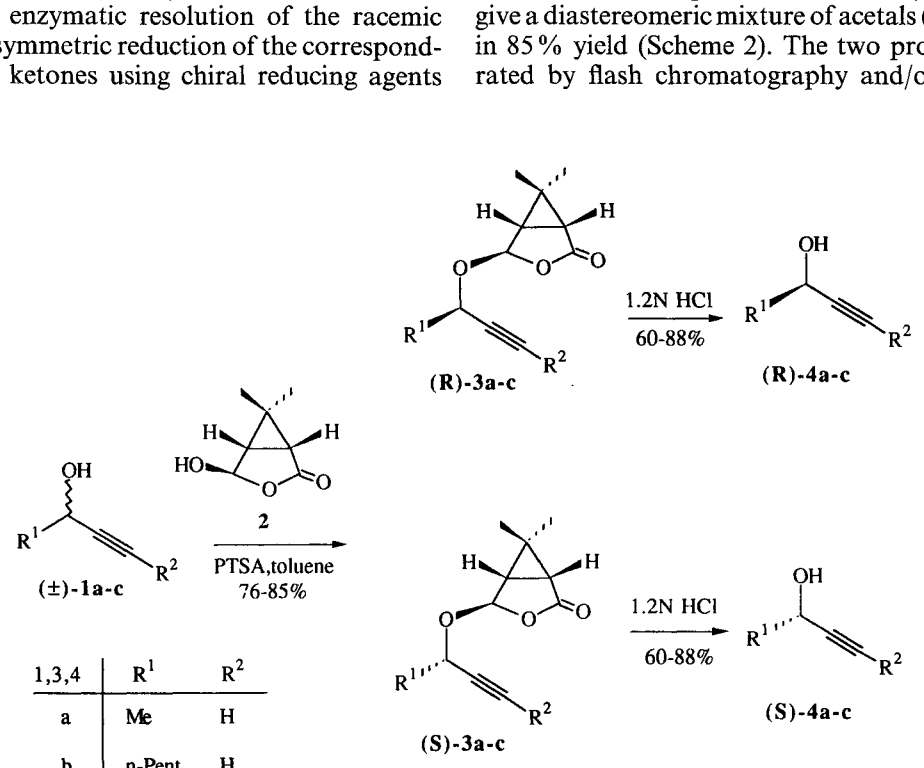
Scheme 1

Optically active alkynyl alcohols are useful intermediates in the synthesis of natural products (e.g. steroids,[3] vitamin E,[4] pheromones,[5] leukotrienes,[6] prostaglandins,[7] antibiotics[8] and alkaloids[9]). They can be obtained either by chemical[10] or enzymatic resolution of the racemic acetates[11] or by asymmetric reduction of the corresponding α,β-acetylenic ketones using chiral reducing agents such as darvon $LiAlH_4$, EtOH, *N*-methylephedrine,[12] alpine borane[13] and (*S*)-Binal-H.[14] In addition to the asymmetric reduction route, optically active propargylic alcohols have been prepared by enantioface-differentiating addition of lithium acetylide to aliphatic aldehydes in the presence of chiral ligands.[15]

In all these cases, the optical purity ranged from moderate to good, with enantioselectivities of up to 99%, but these methods[16] did not allow the preparation of both enantiomers on a preparative scale.

We report herein a practical method for the resolution of racemic alkynyl alcohols by formation of diastereomeric acetals **3** with 4-hydroxy-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one **2** (biocartol) available from the industrial synthesis of chrysanthemic acid. We initially examined the acetalisation of racemic but-1-yn-3-ol **1a** with biocartol **2**. This resolving agent has been shown to be highly effective in the resolution of several racemic alcohols occurring in synthetic pyrethroids.[17] This useful two-step resolution of secondary racemic alcohols has also been successfully used in the synthesis of lineatin.[18]

In the presence of a catalytic amount of *p*-toluenesulfonic acid, the reaction proceeded smoothly in two hours to give a diastereomeric mixture of acetals (*R*)-**3a** and (*S*)-**3a** in 85% yield (Scheme 2). The two products were separated by flash chromatography and/or medium liquid



1,3,4	R^1	R^2
a	Me	H
b	n-Pent	H
c	i-Bu	Me

Scheme 2

pressure chromatography and subjected to hydrolysis using HCl (1.2 N) in diethyl ether for 5 days to give, after distillation, optically pure butynols (*R*)-**4a** and (*S*)-**4a** in 60% yield. Analysis of the products by gas chromatography using chiral column chromatography (Lipodex A) indicated an enantiomeric excess of > 99% of (*R*)-**4a** and (*S*)-**4a**.

We next examined the resolution of oct-1-yn-3-ol **(1b)** and 6-methylhept-2-yn-4-ol **(1c)** under the same conditions. As expected, the reactions were complete in 2 hours and afforded the desired products (*R*)-**3b**, (*S*)-**3b** and (*R*)-**3c**, (*S*)-**3c** in 76% and 80% yield, respectively. These acetals furnished the acetylenic alcohols (*R*)-**4b**, (*R*)-**4c** and (*S*)-**4c**, respectively, in yields of 88% and 86% after hydrolysis for 2 hours at room temperature. GC analysis of these materials on a chiral column, as described in the experimental section, revealed an enantiomeric excess of > 99% for each alcohol and each enantiomer.

In conclusion, biocartol **2** is an attractive reagent for the resolution of the sensitive racemic propargylic alcohols. The overall yields of the optically pure materials obtained by this two-step sequence are good and the method, easy to perform, has been carried out on a multigram scale. In addition, the biocartol **2** can be recycled.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 200. MS data were recorded on a Hewlett Packard 5989 A instrument. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 589 nm. IR spectra were recorded on a IRFT 45 Bruker. Chiral GC chromatography was performed on a Lipodex A Macherey Nägel column. Microanalyses were obtained from P. et M. Curie University Microanalysis Laboratory. Satisfactory microanalyses results (C,H ± 0.10) were obtained for (*R*)- and (*S*)-**3a**.

Formation of the Lactonic Acetals; General Procedure:
The alkynyl alcohol, 1 equiv of biocartol **2** and 1% of *p*-TsOH were refluxed in toluene (3.5 l/mol) for 2 hours with azeotropic removal of H_2O using a Dean–Stark apparatus. After quenching with Et_3N, the solvent was evaporated under reduced pressure and the residue was subjected to chromatography (Art 11567 Merck silica gel; 0.040–0.063 mm).

Hydrolysis of the Lactonic Acetals; General Procedure:
The diastereomeric ether was stirred for 2 to 5 days at 20°C in a mixture of 1.2 N HCl (0.18 equiv) and Et_2O (1.2 L/mol) or THF (1.2 L/mol). The aq layer was saturated with NH_4SO_4 salt and extracted with Et_2O. After washing with sat. aq $NaHCO_3$ and drying (Na_2SO_4), the alcohol was distilled under reduced pressure. The biocartol **2** was recovered by crystallization from a mixture of Et_2O/pentane.

(1R,4R,5S)-6,6-Dimethyl-4-[(R)-3-but-1-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one(R)-**3a**:

11 mL (0.142 M) of butynol (±)-**1a** and 20 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 5:95) 9.3 g of (*R*)-**3a**; $R_f = 0.27$ (EtOAc/cyclohexane 1:9); yield: 34%; mp = 55°C; $[\alpha]_D^{20} = -140$ ($c = 1$, $CHCl_3$).

IR (KBr): $\nu = 2210, 1765, 1350\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.54 (d, 3H, $J = 7.1$ Hz, $CHC\underline{H}_3$), 2.06 (d, 1H, $J = 5.8$ Hz, $C\underline{H}CH$), 2.11 (d, 1H, 5.8 Hz, $C\underline{H}C{=}O$), 2.56 (d, 1H, $J = 2$ Hz, $\equiv C\underline{H}$), 4.60 (dq, 1H, $J = 7.1$, 2 Hz, $CHC\equiv$), 5.40 (s, 1H, OCHO).

^{13}C NMR ($CDCl_3$): $\delta = 14.98$, 21.77 ($2CH_3$), 24.50 [$\underline{C}(CH_3)_2$], 25.31 ($CH\underline{C}H_3$), 29.67 (CHCH), 35.17 ($\underline{C}HC{=}O$), 62.89 (OCHO), 74.10 ($\underline{C}HC\equiv$), 82.07 ($C\equiv\underline{C}H$), 98.20 ($\underline{C}\equiv CH$), 173.07 (C=O).

MS: $m/z = 193\ (M-1)^+$.

(1R,4R,5S)-6,6-Dimethyl-4-[(S)-3-(but-1-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one (S)-**3a**:

11 mL (0.142 M) of butynol (±)-**1a** and 20 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 5:95) 14 g of (*S*)-**3a**; $R_f = 0.32$ (EtOAc/cyclohexane 1:9); yield: 51%; mp = 85–87°C; $[\alpha]_D^{20} = -311$ ($c = 1$, $CHCl_3$).

IR (KBr): $\nu = 2190, 1765, 1360\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 1.19$ (s, 3H), 1.23 (s, 3H), 1.5 (d, 3H, $J = 7$ Hz), 2.04 (d, 1H, $J = 5.7$ Hz), 2.11 (d, 1H, 5.7 Hz), 2.52 (d, 1H, $J = 2$ Hz), 4.61 (dq, 1H, $J = 7.2$ Hz), 5.51 (s, 1H).

^{13}C NMR ($CDCl_3$): $\delta = 15.00$, 21.75, 24.53, 25.30, 29.67, 35.17, 62.89, 74.11, 82.06, 98.20, 173.15.

MS: $m/z = 193\ (M-1)^+$.

(1R,4R,5S)-6,6-Dimethyl-4-[(R)-3-(oct-1-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one (R)-**3b**:

10.22 mL (0.071 M) of oct-1-yn-3-ol (±)-**1b** and 10 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 1:9) 5.2 g of (*R*)-**3b**; $R_f = 0.65$ (EtOAc/cyclohexane 1:5); yield: 30%; $[\alpha]_D^{20} = -64.8$ ($c = 1$, dioxane).

IR (neat): $\nu = 2200, 1765\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 0.9$ (t, 3H, $J = 6.6$ Hz, $C\underline{H}_3CH_2$), 1.15 (s, 3H, CCH_3), 1.20 (s, 3H, CCH_3), 1.20–1.85 [m, 8H, $(C\underline{H}_2)_4CH_3$], 2.05 (dd, 1H, $J = 5.7$, 0.8 Hz, $C\underline{H}CHO_2$), 2.10 (d, 1H, $J = 5.7$ Hz, $CHC{=}O$), 2.5 (d, 1H, $J = 2$ Hz, $\equiv CH$), 4.4 (m, 1H, $CHC\equiv$), 5.4 (s, 1H, OCHO).

^{13}C NMR ($CDCl_3$): $\delta = 13.86$ ($\underline{C}H_3CH_2$), 14.99, 22.36 [$C(\underline{C}H_3)_2$], 24.36, 25.28, 29.70, 31.21 ($4\times CH_2$), 35.12 ($\underline{C}HCH$), 35.18 ($\underline{C}HC{=}O$), 67.09 ($\underline{C}HC\equiv$), 74.76 (OCHO), 81.35 ($C\equiv\underline{C}H$), 98.26 ($\underline{C}\equiv CH$), 173.28 (C=O).

MS: $m/z = 249\ (M-1)^+$.

(1R,4R,5S)-6,6-Dimethyl-4-[(S)-3-(oct-1-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one (S)-**3b**:

10.22 mL (0.071 M) of oct-1-yn-3-ol (±)-**1b** and 10 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 1:9) 8 g of (*S*)-**3b**; $R_f = 0.75$ (EtOAc/cyclohexane 1:5); yield: 46%; $[\alpha]_D^{20} = -193$ ($c = 1$, dioxane).

IR (neat): $\nu = 2210, 1765\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 0.9$ (t, 3H, $J = 6.6$ Hz), 1.15 (s, 3H), 1.20 (s, 3H), 1.20–1.85 (m, 8H), 2.0 (dd, 1H, $J = 5.7$, 0.8 Hz), 2.10 (d, 1H, $J = 5.7$ Hz), 2.5 (d, 1H, $J = 2$ Hz), 4.5 (m, 1H), 5.5 (s, 1H).

^{13}C NMR ($CDCl_3$): $\delta = 13.50$, 15.01, 22.35, 24.40, 25.25, 29.80, 31.24, 35.10, 35.14, 67.11, 75.01, 81.30, 98.20, 173.29.

MS: $m/z = 249\ (M-1)^+$.

(1R,4R,5S)-6,6-Dimethyl-4-[(S)-4-(6-methylhept-2-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one (S)-**3c**:

18 g (0.14 M) of 6-methylhept-2-yn-4-ol (±)-**1c** and 20 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 1:9) 11.5 g of (*R*)-**3c**; $R_f = 0.74$ (EtOAc/cyclohexane 1:5); yield: 32%; $[\alpha]_D^{20} = -21$ ($c = 1$, dioxane).

IR (neat): $\nu = 2980, 2930, 2870, 2240, 1775, 1470, 1350, 1170\ cm^{-1}$.

^{1}H NMR ($CDCl_3$): $\delta = 0.85$–0.90 [2d, 6H, $J = 5.5$ Hz, $CH(C\underline{H}_3)_2$], 1.1 (s, 3H, CCH_3), 1.2 (s, 3H, CCH_3), 1.4–1.8 [m, 3H, $(CH_3)_2C\underline{H}C\underline{H}_2$)], 1.9 (d, 3H, $J = 2$ Hz, $\equiv CCH_3$), 2.05 (d, 1H, $J = 5$ Hz, $C\underline{H}CH$), 2.1 (d, 1H, $J = 5$ Hz, $C\underline{H}C{=}O$), 4.4 (m, 1H, $CHC\equiv$), 5.4 (s, 1H, OCHO).

^{13}C NMR ($CDCl_3$): $\delta = 3.52$ ($\equiv C\underline{C}H_3$), 15.03, 22.25 [$C(\underline{C}H_3)_2$], 24.46, 25.30 [$(CH_3)_2\underline{C}H\underline{C}H_2$], 26.78 [$\underline{C}(CH_3)_2$], 29.74 ($\underline{C}HCH$), 35.25 ($\underline{C}HC{=}O$), 44.54 ($\underline{C}HC\equiv$), 66.26 (OCHO), 82.70 ($\equiv\underline{C}CH_3$), 98.18 ($\underline{C}\equiv CCH_3$), 173.32 (C=O).

MS: $m/z = 249\ (M-1)^+$.

(1R,4R,5S)-6,6-Dimethyl-4-[(S)-4-(6-methylhept-2-ynyloxy)]-3-oxabicyclo[3.1.0]hexan-2-one (S)-**3c**:

18 g (0.14 M) of 6-methylhept-2-yn-4-ol (±)-**1c** and 20 g of biocartol **2** afforded after chromatography (EtOAc/cyclohexane 1:9) 17.1 g of (S)-**3c**; $R_f = 0.5$ (EtOAc/cyclohexane 1:5); yield: 48%; $[\alpha]_D^{20} = -246.9$ ($c = 1$, dioxane).

IR (neat): ν = 2980, 2930, 2870, 2240, 1775, 1470, 1350, 1170 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.90–0.95 (2d, 6H, J = 5.3 Hz), 1.2 (s, 3H), 1.3 (s, 3H), 1.5–1.9 (m, 3H), 1.9 (d, 3H, J = 2 Hz), 2.0 (d, 1H, J = 5 Hz), 2.1 (d, 1H, J = 5 Hz), 4.5 (m, 1H), 5.5 (s, 1H).

^{13}C NMR ($CDCl_3$): δ = 3.50, 15.02, 22.25, 24.45, 25.40, 26.75, 29.74, 35.25, 44.40, 66.27, 82.90, 98.21, 173.30.

MS: m/z = 249 $(M-1)^+$.

(2R)-But-1-yn-3-ol (R)-**4a**:

From the hydrolysis of 9.3 g of (R)-**3a** for 5 days in Et_2O, after distillation, 1.8 g of (*R*)-**4a** were obtained; bp = 100 °C/130 mmHg; yield: 55 %; $[\alpha]_D^{20}$ = + 44 (c = 1.2, dioxane).

IR (neat): ν = 3400, 3300, 2990, 2940, 2840, 2120 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.5 (d, 3H, J = 6.6 Hz, CH_3), 1.92 (d, 1H, J = 5.5 Hz, OH), 2.51 (d, 1H, J = 2.2 Hz, C≡CCH), 4.50 (m, 1H, CHOH).

^{13}C NMR ($CDCl_3$): δ = 24.01 (CH_3), 58.08 (CHOH), 71.98 (C≡C<u>C</u>H), 85.60 (<u>C</u>≡CCH).

MS: m/z = 69 $(M-1)^+$

GC: temp = 35 °C, rate = 1 d°/min., RT = 10.04 min.
ee ≈ 100 %.

(2S)-But-1-yn-3-ol (S)-**4a**:

From the hydrolysis of 13 g of (*S*)-**3a** for 5 days in Et_2O, after distillation, 2.8 g of (*S*)-**4a** were obtained; bp = 100 °C/130 mmHg: yield: 60 %; $[\alpha]_D^{20}$ = − 41 (c = 3.45, dioxane).

GC: RT = 10.39 min.

ee ≈ 100 %.

(2R)-Oct-1-yn-3-ol (R)-**4b**:

From the hydrolysis of 4 g of (*R*)-**3b** for 2 days in THF, after distillation, 1.5 g of (R)-**4b** were obtained; bp = 75 °C/14 mmHg; yield: 60 %; $[\alpha]_D^{20}$ = + 14.86 (c = 1, dioxane).

IR (neat): ν = 3400, 3310, 2960, 2930, 2860, 2110, 1470 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, 3H, J = 6.6 Hz, $C\underline{H}_3CH_2$), 1.1–1.72 [m, 8H, $CH_3(CH_2)_4$], 2.15 (d, 1H, J = 5.2 Hz, OH), 2.4 (d, 1H, J = 2 Hz, C≡CCH), 4.3 (m, 1H, C<u>H</u>OH).

^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 22.45, 24.58, 31.35, 37.5 (4 × CH_2), 62.24 (CHOH), 72.65 (C≡C<u>C</u>H), 84.90 (<u>C</u>≡CCH).

MS: m/z = 125 $(M-1)^+$.

GC: temp = 70 °C, rate = 0.5 d°/min., RT = 23.76 min.

ee ≈ 100 %.

(2S)-Oct-1-yn-3-ol (S)-**4b**:

From the hydrolysis of 6 g of (*S*)-**3b** for 2 days in THF, after distillation, 2.5 g of (*S*)-**4b** were obtained; bp = 75 °C/14 mmHg; yield: 88 %; $[\alpha]_D^{20}$ = − 15.7° (c = 1, dioxane).

GC: RT = 23.52 min.

ee ≈ 100 %.

(4R)-6-Methylhept-2-yn-4-ol (R)-**4c**:

From the hydrolysis of 5 g of (*R*)-**3c** for 2 days in THF, after distillation, 2.2 g of (*R*)-**4c** were obtained: bp = 60 °C/3 mmHg; yield: 87 %; $[\alpha]_D^{20}$ = 25.12 (c = 1.6, dioxane)

IR (neat): ν = 3350, 2960, 2915, 2890, 2260, 2220, 1470 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80–0.85 [2d, 6H, J = 5.4 Hz, $C(CH_3)_2$], 1.55 [m, 3H, $(CH_3)_2C\underline{H}C\underline{H}_2$], 1.75 (d, 3H, J = 2.7 Hz (≡CCH_3), 2.25 (s, 1H, OH), 4.3 (m, 1H, C<u>H</u>OH).

^{13}C NMR ($CDCl_3$): δ = 3.35 (C≡C<u>C</u>H_3), 22.35, 24.59 (2 × CH_3, CH, CH_2), 47.03 (CHOH), 60.97 (C≡<u>C</u>CH_3), 80.62 (<u>C</u>≡CCH_3).

MS: m/z = 125 $(M-1)^+$.

GC: temp = 60 °C, rate = 2 d°/min., RT = 9.23 min.

ee ≈ 100 %.

(4S)-6-Methylhept-2-yn-4-ol(S)-**4c**:

From the hydrolysis of 5 g of (*S*)-**3c** for 2 days in THF, after distillation, 2.1 g of (*S*)-**4c** were obtained; bp = 60 °C/3 mmHg; yield: 85 %; $[\alpha]_D^{20}$ = − 27.25 (c = 4.3, dioxane)

GC: RT = 8.91 min.

ee ≈ 100 %.

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