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Efficient stereoselective synthesis of enantiopure 2-substituted paraconic acids

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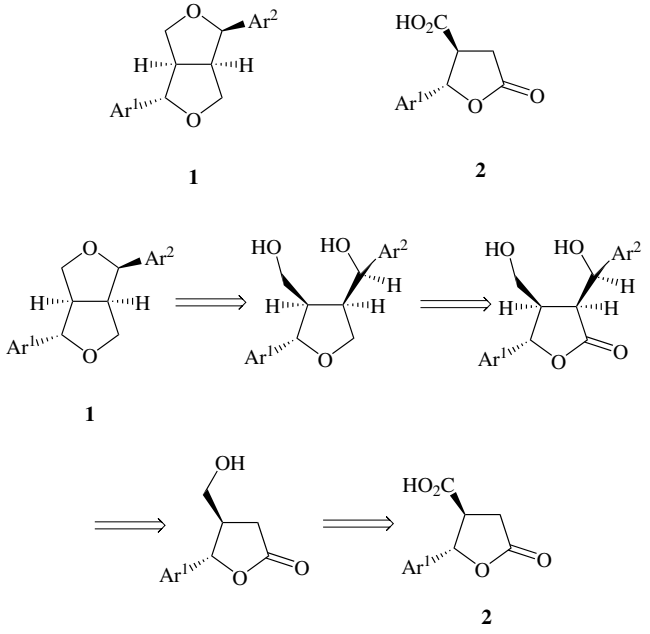
Abstract—Eight enantiopure (2*S*,3*S*)-2-aryl-5-oxotetrahydrofuran-3-carboxylic acids have been synthesized. The key step was a highly stereoselective aldol reaction between an *N*-acyl oxazolidinone and a corresponding aldehyde.

1. Introduction

Paraconic acids are a family of chiral γ-butyrolactones with a carboxylic acid at the β-position, isolated from various species of *mosses, lichens*, and *fungus*. They possess important biological activities, such as antitumor, antibiotic, antifungal, and antibacterial.[1] Racemic, as well as enantioselective syntheses of several paraconic acids have already been reported.[2] However, many of these suffer from poor overall yields, large number of steps, and a lack of generality. Furofurans, one of the major subclasses of the lignan family, exhibit a wide variety of biological activities, such as antitumor, antihypertensive, antioxidant, inhibition of plate-activating factor (PAF), phosphodiesterase inhibitory activity on microsomal monooxygenase in insects, and pyrenthrins insecticidal.[3]

Due to the important biological activities of paraconic acids, many publications have represented interesting methods for their stereoselective syntheses,[4] including the ring-closing methathesis of two electron deficient olefins,[5] free radical-mediated conjugate additions,[6] and aldol reactions of dioxones derived from tartaric acid.[7] Of the furofurans, unsymmetrically substituted furofurans **1**, such as (+)-fargesin, (+)-epimagnolin, and (+)-kobusin have generated considerable and continued interest due to their unique structural characteristics and stereochemical diversity. For the synthesis of those compounds, enantiopure 2-substituted paraconic acid **2** is a key starting material (Scheme 1). Lawlor and McNamee[8] reported the synthesis of *trans* 2-substituted paraconic acid, together with its *cis*-isomer (3:2 overall 75%).

In connection with our synthetic studies for unsymmetrically substituted furofurans, we herein report an efficient stereoselective synthesis of enantiopure 2-substituted



Scheme 1. Retrosynthetic analysis of **1**.

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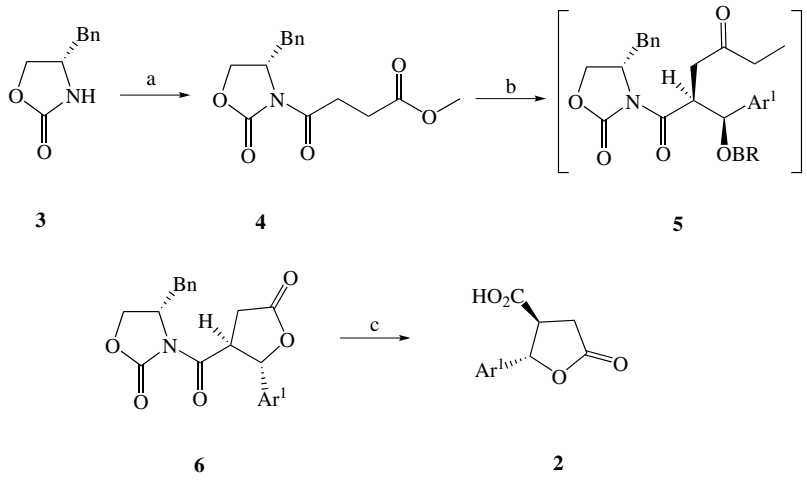
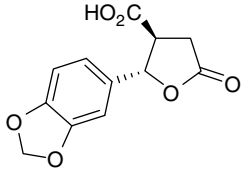
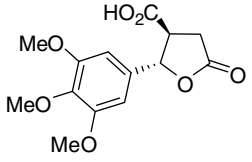
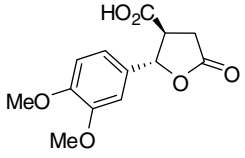
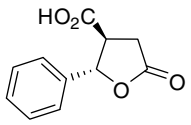
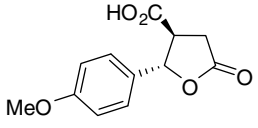


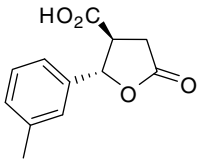
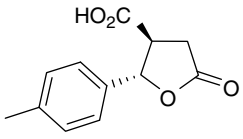
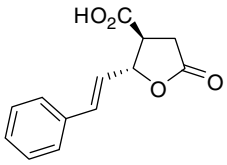
Scheme 2. Reagents and conditions: (a) *n*-BuLi, β-carbomethoxypropionyl chloride/THF, −78 °C to rt, 3 h; (b) Bu_2BOTf, DIPEA/CH_2Cl_2, −78 °C, Ar_1CHO, 20 min; (c) LiOH, H_2O_2/THF:H_2O, 0 °C to rt, 3 h.

Table 1. Physical and spectroscopic data of 2-substituted paraconic acids

Entry	Products	Yield[a] physicochemical properties	IR (neat, cm^{-1})	HRMS	NMR
1		Yield: 65% mp (°C): 160–161 $[\alpha]_D^{25} = -44.2$ (*c* 1.0, MeOH)	3428, 1782, 1736, 1170	Calcd for $C_{12}H_{11}O_6$ 251.0556 $[M+H]^+$, found 251.0567	^1H NMR (300 MHz, CD_3OD): δ 2.97 (m, 2H), 3.41 (m, 1H), 5.56 (d, $J = 7.79$ Hz, 1H), 5.97 (s, 2H), 6.72–6.92 (m, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.1, 174.0, 149.6, 133.4, 121.3, 109.1, 107.4, 102.7, 84.5, 49.6, 33.5
2		Yield: 48% mp (°C): 143–145 $[\alpha]_D^{25} = -36.2$ (*c* 1.0, MeOH)	3479, 1778, 1735, 1126	Calcd for $C_{14}H_{16}O_7$ 296.0896 $[M+H]^+$, found 296.0998	^1H NMR (300 MHz, CD_3OD): δ 2.70 (m, 2H), 3.33 (m, 1H), 3.77 (s, 9H), 5.56 (d, $J = 6.70$ Hz, 1H), 6.53 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.1, 174.1, 154.8, 135.8, 104.4, 104.3, 84.4, 61.1, 56.7, 56.6, 49.7, 33.4
3		Yield: 67% mp (°C): 178–179 $[\alpha]_D^{25} = -29.4$ (*c* 1.0, MeOH)	3386, 1743, 1643, 1176	Calcd for $C_{13}H_{15}O_6$ 267.0869 $[M+H]^+$, found 267.0775	^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (m, 2H), 3.44 (m, 1H), 3.81 (d, $J = 1.10$ Hz, 6H), 5.60 (d, $J = 7.26$ Hz, 1H), 6.80 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 173.8, 149.8, 129.9, 118.2, 111.1, 108.4, 82.1, 56.0, 48.1, 32.3
4		Yield: 57% mp (°C): 119–123 $[\alpha]_D^{25} = -37.4$ (*c* 1.6, MeOH)	3413, 1747, 1643, 1191	Calcd for $C_{11}H_{11}O_4$ 207.0657 $[M+H]^+$, found 207.0676	^1H NMR (300 MHz, CD_3OD): δ 2.80 (m, 2H), 3.41 (m, 1H), 5.60 (d, $J = 7.41$ Hz, 1H), 7.30–7.391 (m, 5H). ^{13}C NMR (75 MHz, CD_3OD): δ 177.2, 174.1, 139.9, 129.9, 129.8, 127.1, 84.4, 49.7, 33.3
5		Yield: 69% mp (°C): 138–139 $[\alpha]_D^{25} = -56.0$ (*c* 1.6, MeOH)	3490, 1785, 1731, 1173	Calcd for $C_{12}H_{13}O_5$ 237.0763 $[M+H]^+$, found 237.0884	^1H NMR (300 MHz, $CDCl_3$): δ 3.02 (m, 2H), 3.41 (m, 1H), 3.80 (s, 3H), 5.60 (d, $J = 7.35$ Hz), 6.90 (m, 2H), 7.32 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 173.9, 132.4, 127.1, 114.3, 113.8, 82.1, 55.4, 48.2, 32.3

(*continued on next page*)

Table 1 (*continued*)

Entry	Products	Yield[a] physicochemical properties	IR (neat, cm^{-1})	HRMS	NMR
6		Yield: 52% mp (°C): 110–113 $[\alpha]_D^{25} = -61.1$ (*c* 1.0, MeOH)	3394, 1747, 1670, 1191	Calcd for $C_{12}H_{13}O_4$ 221.0814 $[M+H]^+$, found 221.0768	^1H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.05 (m, 2H), 3.30–3.44 (m, 1H), 5.60 (d, $J = 6.60$ Hz, 1H), 7.06–7.30 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 174.3, 138.8, 137.6, 129.8, 128.8, 125.9, 122.5, 82.0, 48.2, 31.8, 21.4
7		Yield: 60% mp (°C): 103–106 $[\alpha]_D^{25} = -31.3$ (*c* 1.0, MeOH)	3428, 1747, 1673, 1195	Calcd for $C_{12}H_{13}O_4$ 221.0814 $[M+H]^+$, found 221.0772	^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.95 (m, 2H), 3.35 (m, 1H), 5.60 (d, $J = 6.87$ Hz, 1H), 7.12–7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.1, 174.1, 139.1, 134.7, 129.6, 125.4, 82.1, 48.2, 32.0, 21.8
8		Yield: 46% mp (°C): 145–146 $[\alpha]_D^{25} = +15.0$ (*c* 1.6, MeOH)	3390, 1778, 1735, 1167	Calcd for $C_{13}H_{13}O_4$ 233.0814 $[M+H]^+$, found 233.0746	^1H NMR (300 MHz, $CDCl_3$): δ 2.70 (dd, $J = 8.60$, 17.7 Hz, 1H), 3.03 (dd, $J = 7.20$, 17.7 Hz, 1H), 3.69 (m, 1H), 5.45 (m, 1H), 6.20 (m, 1H), 6.79 (d, $J = 15.8$ Hz, 1H), 7.2–7.3 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 174.5, 135.3, 134.9, 128.7, 126.9, 121.5, 79.8, 31.0, 29.7

[a] Isolated yield based on compound **4**.

paraconic acids **2**. The key reaction is a highly stereoselective aldol reaction between an *N*-acyl oxazolidinone and a suitable aldehyde.

2. Results and discussion

The synthesis of (2*S*,3*S*)-2-aryl-5-oxotetrahydrofuran-3-carboxylic acids **2** was accomplished as depicted in Scheme 2.

β-Carbomethoxypropionyl chloride was treated with freshly prepared (*S*)-(−)-4-benzyl-2-oxazolidinone **3** (reduction of (*S*)-phenylalanine with sodium borohydride gave (*S*)-phenylalaninol, which upon treatment with anhydrous sodium carbonate in diethyl carbonate gave an oxazolidinone, 80% yield over two steps[9]), in the presence of *n*-BuLi to afford 1-(4*S*-benzyl-2-oxazolidin-3-yl)-4-methoxybutane-1,4-dione **4** in 95% yield. Aldol condensation of a boron (*Z*)-enolate[10] (generated by the treatment of *N*-acyl oxazolidinone **4** with dibutylboron triflate[11] and DIPEA in CH_2Cl_2 at −78 °C), followed by treatment with the corresponding aldehyde, afforded the addition product **5** as an unstable key intermediate, which was not isolated but instead subjected to intramolecular ring cyclization to give γ-lactone **6** with 95:5 diastereomeric selectivity, which was determined on the basis of HPLC analysis.[12] The chiral auxiliary was removed using lithium peroxide[13] to afford (2*S*,3*S*)-2-aryl-5-oxotetrahydrofuran-3-carboxylic acids **2**. Eight (2*S*,3*S*)-2-aryl-5-oxotetrahydrofuran-3-carboxylic acids were prepared. Their physical and spectral data are given in Table 1.

3. Conclusion

In conclusion, we have presented a short, general, and efficient approach to the synthesis of enantiopure 2-substituted paraconic acids. By using this methodology, (+)-fargesin and (+)-epimagnolin were synthesized.[14]

Acknowledgment

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