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Solution-Phase and Solid-Phase Syntheses of Enzyme Inhibitor RK-682 and Antibiotic Agglomerins

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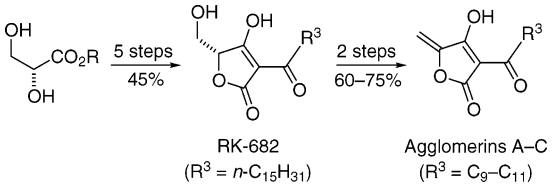
Received April 19, 2005

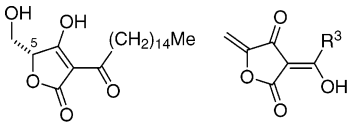


RK-682 (R^3 = *n*-$C_{15}H_{31}$)

Agglomerins A–C (R^3 = C_9–C_{11})

The enzyme inhibitor RK-682 (5*R*)-(+)-**1** was prepared in solution and on a solid support from (2*R*)-glycerates in five steps and ca. 40% overall yield. Key steps were a ring-closing tandem addition−Wittig alkenation reaction of the respective protected or immobilized glycerates with the ylide Ph_3-PCCO and the 3-acylation of the tetronic acids thus obtained with palmitic acid. A similar route extended by a mesylation−elimination sequence led to antibiotic agglomerins A−C **2** featuring 3-acyl-5-methylidenetetronic acid structures.

Physiologically active tetronic acids have been isolated from a broad range of organisms such as molds, fungi, lichens, and sponges.[1−3] RK-682 (*5R*)-**1** is a typical example of 3-acyltetronic acids bearing short hydrophilic residues at C-5. It was isolated as the corresponding tetronate salts with different countercations from the strains *Actinomycetes* DSM 7357 by a CIBA-GEIGY group,[4] from *Streptomyces* sp. 88-682 by a RIKEN group,[5] and from *Streptomyces* sp. AL-462 by a TAKEDA group.[6] It was found to inhibit HIV-1 protease[4] and various other protein tyrosine kinases and phosphatases[7] presumably by acting as a phosphate mimic. Early stereoselective syntheses by the TAKEDA group[6] and others[3d,8] served to ascertain the absolute configuration of the natural products. Recently, a library of congeners of **1** with diversity in the 3- and the 5-residues was built up via a Lacey−Dieckmann-based[9] solution-phase synthesis and screened for inhibition of the phosphatases VHR and cdc25B.[10] Other structural variations have also been published.[11] Agglomerins A−D **2** are antibiotics mainly active against anaerobic bacteria, both Gram-positive and Gram-negative. They are produced[12] by *Enterobacter agglomerans* PB-6042 in a biosynthetic route closely resembling that for RK-682.[13]



R-**1**: RK-682 **2**: Agglomerins

	R^3
A	$Me(CH_2)_8$
B	$H_3C(CH_2)_5CHCH(CH_2)_3$
C	$Me(CH_2)_{10}$
D	$H_3C(CH_2)_6CHCH(CH_2)_4$

Herein we report an efficient six-step solution-phase synthesis of RK-682 (*5R*)-**1** from glycerate **4** (Scheme 1) and a solid-phase variant thereof (Scheme 3), which should be widely applicable to 5-substituted 3-alkanoyltetronic acids in general, lending itself ideally to a combinatorial processing. We also describe an extended synthetic route leading to agglomerins A−C (Scheme 2).

Commercially available methyl isopropylidene-D-glycerate **3** was converted to the benzyl ester **4** according to a method by Giannis et al.[14] After acidic cleavage of the ketal of **4**, the terminal hydroxy group of the product **5** was tritylated to give α-hydroxy ester **6**. The latter was then cyclized under pH-neutral, nonracemizing conditions to the corresponding tetronate **7** using the readily available phosphorus ylide (triphenylphosphoranylidene)-ketene, $Ph_3P{=}C{=}C{=}O$.[15] When conducted under microwave irradiation, the reaction was complete after 1 h, furnishing a satisfactory 75% yield of **7**. Mechanistically, it commences with an addition of the OH group of **6**

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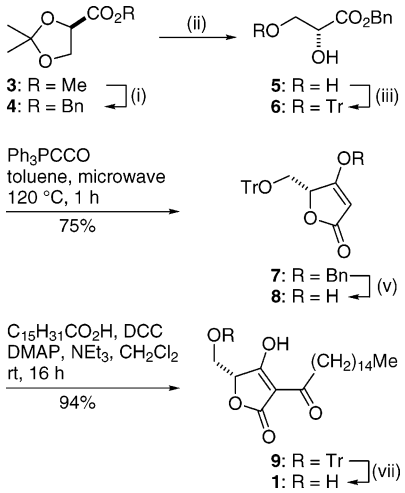
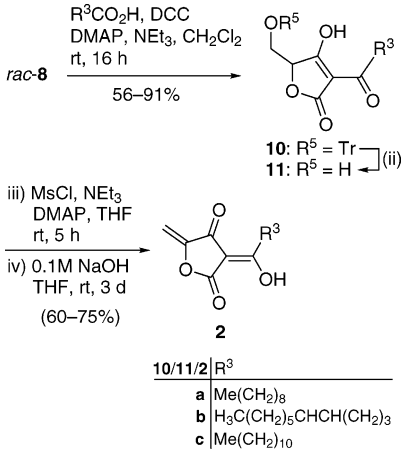
10.1021/jo050797i CCC: $30.25
Published on Web 06/25/2005

SCHEME 1. Solution-Phase Synthesis of RK-682 (5*R*)-(+)-1[a]



[a] Reagents and conditions: (i) BnOH, Bu_2SnO, microwave, 120 °C, 30 min, 83%; (ii) 1 M HCl, THF, rt, 12 h, 85%; (iii) TrCl, NEt_3, DMAP, CH_2Cl_2, rt, 8 h, 80%; (iv) shown above; (v) 5% Pd/C, H_2 (1 bar), THF, rt, 3 h, 99%; (vi) shown above; (vii) 1 M HCl, MeOH, rt, 48 h, 79%.

SCHEME 2. Solution-Phase Synthesis of Agglomerins A−C (2)[a]



10/11/2	R^3
a	$Me(CH_2)_8$
b	$H_3C(CH_2)_5CHCH(CH_2)_3$
c	$Me(CH_2)_{10}$

[a] Reagents and conditions: (i) shown above; (ii) 1 M HCl, MeOH, rt, 48 h, 86%; (iii and iv) shown above.

across the C=C bond of the cumulated ylide to give a stabilized ester ylide, which in turn undergoes an intramolecular olefination of the C=O bond of the benzyl ester moiety. Debenzylation of **7** with H_2 gas using 5% Pd on charcoal as a catalyst afforded the free tetronic acid **8** in quantitative yield. Compound **8** was subsequently acylated at C-3 with palmitic acid according to the protocol by Yoshii et al. (DCC, DMAP, NEt_3).[16] The product 3-palmitoyltetronic acid **9** was obtained in 94% yield. It was finally deprotected with hydrochloric acid to give optically pure RK-682 (*5R*)-(+)-**1** in ca. 40% overall yield with respect to glycerate **4**. This is a 10% improvement on the yield of the synthesis by the Sodeoka group,[3d] who also started from a tritylated glycerate that was acylated to an *O*-(*β*-palmitoacetyl) derivative prior to a Lacey−Dieckmann cyclization. Palmitic acid could not be used directly with this method but required preactivation as a *β*-ketothio ester.

Acyl residues other than palmitoyl were likewise attached to C-3 of tetronic acid **8**, among them various isomeric branched methyldodecanoyl groups. These had been found to confer particularly high bioactivity to the so-called melophlins, a family of naturally occurring 3-acyltetramic acids.[17] Synthetic details and bioscreening results concerning these analogues of **1** will be disclosed elsewhere. The same general approach as outlined in Scheme 1 was also employed in a straightforward synthesis of agglomerins A−C. Racemic tetronic acid *rac*-**8** was prepared from cheap racemic glycerate *rac*-**5** in virtually identical yields when compared to the synthesis of enantiopure (5*R*)-**8**. The required 3-acyl side-chains were introduced by reaction of *rac*-**8** with the respective carboxylic acids, once more under Yoshii conditions. The resulting racemic tetronic acids **10** were deprotected with hydrochloric acid to furnish compounds **11**, which in turn were finally converted in 60−75% yield to the corresponding agglomerins **2** by a mesylation−elimination sequence[10a] (Scheme 2).

Next we sought to transfer the synthesis of RK-682 and analogues as outlined in Scheme 1 to the solid phase to open access to corresponding libraries. In a first attempt, the benzyl ester **5** was immobilized by etherification of its primary OH group with a trityl chloride-tagged polystyrene resin (100−200 mesh, 1% divinyl benzene, loading 1.7 mmol/g), and the resulting resin-bound ester was cyclized with Ph_3PCCO in analogy to the above solution-phase synthesis. However, neither heterogeneous (Pd on charcoal) nor homogeneous (Wilkinson) catalysts were capable of removing the benzyl group from the immobilized tetronate congener of **7** probably due to steric shielding by the resin folds. A better protecting group was found in the trimethylsilylethyl (TMSE) residue. Carboxylic acid **12** as obtained from hydrogenolysis of the benzyl ester **4** was esterified with *O*-trimethylsilylethyl-*N*,*N*′-dicyclohexylisourea[18] to give TMSE ester **13**, which was hydrolyzed to the diol **14** (Scheme 3). Attachment of the latter to the trityl polystyrene resin via DMAP-catalyzed etherification led to α-hydroxyester **15**. Completion of this and all other steps involving resin-bound species was ascertained by the weight increase and by the disappearance of indicative IR bands of the respective precursors. Ring-closing domino addition−Wittig alkenation of **15** to give **16** was carried out in THF at 60 °C instead of toluene at 120 °C to allow for better swelling and to avoid thermal decomposition of the resin. The TMSE group was then selectively removed with TBAF without affecting the trityl linker. The immobilized tetronic acid product **17** is a valuable entry point to the construction of libraries of analogues of RK-682 with diversity in the 3-alkanoyl

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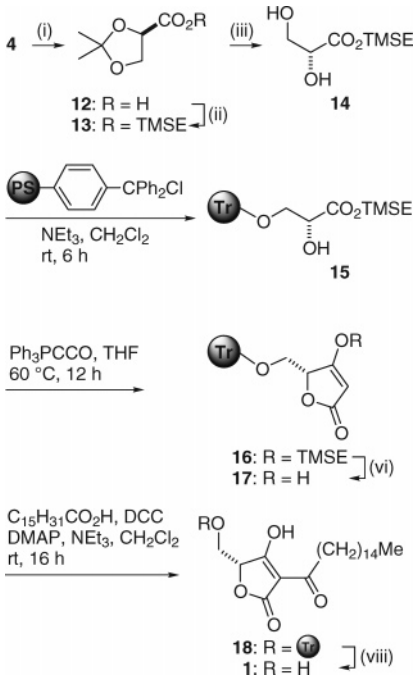
SCHEME 3. Solid-Phase Synthesis of RK-682 (5*R*)-(+)-1[a]



[a] Reagents and conditions: (i) 5% Pd/C, H_2 (1 bar), MeOH, rt, 1 h, 99%; (ii) cycN=C[O(CH$_2$)$_2$SiMe$_3$]NHcyc, THF, 50 °C, 12 h, 74%; (iii) 1 M HCl, MeOH, rt, 12 h, 70%; (iv and v) shown above; (vi) THF, TBAF·3H_2O, rt, 3 h; (vii) shown above; (viii) TFA/Et_3SiH/CH_2Cl_2 (5:5:90), rt, 20 min, 26% (with respect to **14**).

residue. With palmitic acid under Yoshii conditions, immobilized 3-acyltetronic acid **18** was obtained and eventually detached from the resin with TFA and Et_3-SiH to leave **1** in 26% overall yield with respect to **14**.

In conclusion, we described a five-step synthesis of optically pure 5-hydroxmethyl-3-acyltetronic acids from monoprotected/-tethered glycerates based upon a Wittig cyclization with Ph_3PCCO and a downstream 3-acylation of the intermediate tetronic acids with the respective carboxylic acids. The solid-phase variant in particular allows for the generation of libraries of derivatives with different 3-acyl residues, the nature of which has been shown to be crucial for the bioactivity in the series of RK-682 analogues, agglomerins, and 1-*N*-analogous melophlins. As the 3-acylation step precedes the final elimination sequence in our synthesis of the agglomerins, bioactivity screening is conveniently and consecutively possible, both of the 5-hydroxymethyl precursors and the end products bearing 5-methylidene residues.

Experimental Section

(5*R*)-4-Benzyloxy-5-(triphenylmethoxy)methyl-[5*H*]furan-2-one (7). A solution of **6** (438 mg, 1.0 mmol) and Ph_3PCCO (393 mg, 1.3 mmol) in dry THF (15 mL) was stirred at room temperature for 2 h under exclusion of air and moisture. The solution was concentrated and the formed ester ylide was purified by filtration over a short plug of silica gel (THF/hexane, 1:1). The eluate was concentrated; the residue was redissolved in toluene (15 mL), and the solution was placed in a microwave oven. With an irradiation of initially 600 W, a temperature ramp from room temperature to 120 °C was passed through within 4 min, and the end temperature was maintained for an additional hour. The solvent was evaporated, and the crude product was purified by column chromatography (CC) on silica gel to leave 347 mg (75%) of white solid **7** (Found: C, 80.38; H, 5.66. $C_{31}H_{26}O_4$ requires C, 80.50; H, 5.67%): mp 154−156 °C; R_f 0.27 (hexane/ethyl acetate 2:1); $[\alpha]_D^{25}$ −31.0 (*c* 0.55, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 1753, 1629, 1490; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.27 (dd, J = 10.4, 3.4 Hz, 1 H), 3.61 (dd, J = 10.4, 2.7 Hz, 1 H), 4.84 (m, 1 H), 4.99 (d, J = 11.7, 1 H), 5.06 (d, J = 11.7, 1 H), 5.27 (s, 1 H), 7.18−7.40 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) 61.4, 74.4, 78.5, 86.5, 90.7, 127.1, 127.8, 127.9, 128.6, 128.8, 128.9, 133.8, 143.4, 172.6, 178.7; *m/z* (EI) 462 (10) [M$^+$], 385 (10), 243 (100), 183 (10), 165 (35), 105 (20), 91 (100).

(5*R*)-5-(Triphenylmethoxy)methyl-[5*H*]furan-2,4-dione (8). A solution of **7** (231 mg, 0.5 mmol) in dry THF (15 mL) was treated with 5% Pd on charcoal (15 mg). The reaction vessel was repeatedly evacuated and flushed with hydrogen gas and left to stir at room temperature for 3 h, pressurized with 1 bar of H_2. The resulting reaction mixture was filtered through a short plug of Celite, which was washed with THF (40 mL). The filtrates were concentrated on an oil pump to give pure tetronic acid **8** (185 mg, 99%) as a white solid (Found: C, 77.35; H, 5.46. $C_{24}H_{20}O_4$ requires C, 77.40; H, 5.41%): mp 54−56 °C; R_f 0.19 (hexane/ethyl acetate 1:1); $[\alpha]_D^{25}$ 36.2 (*c* 0.54, $CHCl_3$); ν_{max} (ATR)/cm^{-1} 3087, 1704, 1684, 1580, 1489, 1449, 703; ^{1}H NMR (300 MHz, acetone-d_6) δ 3.30 (dd, J = 10.4, 3.8 Hz, 1 H), 3.57 (dd, J = 10.4, 2.7 Hz, 1 H), 4.98 (m, 1 H), 5.11 (s, 1 H), 7.15−7.50 (m, 15 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 62.9, 79.0, 87.2, 91.1, 128.1, 128.8, 129.5, 144.7, 173.6, 179.2; *m/z* (EI) 372 (30) [M$^+$], 295 (30), 243 (100), 183 (30), 165 (55), 105 (70).

(5*R*)-3-Hexadecanoyl-5-(triphenylmethoxy)methyl-[5*H*]-furan-2,4-dione (9). NEt_3 (0.07 mL, 0.5 mmol) was added at 0 °C to a stirred suspension of tetronic acid **8** (160 mg, 0.45 mmol) in anhydrous CH_2Cl_2 (15 mL). To the resulting homogeneous solution was added in succession DMAP (20 mg), palmitic acid (128 mg, 0.5 mmol), and DCC (113 mg, 0.55 mmol) in three portions. The mixture was stirred for 10 min at 0 °C; the cooling bath was removed, and stirring was continued for 16 h at room temperature. The precipitate *N*,*N*′-dicyclohexylurea was filtered off over a short plug of Celite, which was washed with ethyl acetate (50 mL). The combined filtrates were washed with 0.5 M aqueous HCl and brine, dried over Na_2SO_4, and concentrated. The crude product was purified by CC on silica gel to leave **9** (259 mg, 94%) as a yellow oil: R_f 0.42 ($CHCl_3$/MeOH 19:1); $[\alpha]_D^{25}$ 47.1 (*c* 0.5, $CHCl_3$) [lit.[7] 48.27 (*c* 1.02, $CHCl_3$)].

(5*R*)-RK-682 (1). A solution of **9** (162 mg, 0.26 mmol) in MeOH (15 mL) was treated with 1 M aqueous HCl (0.26 mL, 0.26 mmol), and the mixture was stirred at room temperature for 48 h. The volatiles were removed in vacuo, and the residue was purified by CC on silica gel ($CHCl_3$/MeOH 1:0, then $CHCl_3$/MeOH 20:1, then $CHCl_3$/MeOH 10:1). The fractions containing product were pooled and concentrated, and the residue was redissolved in ethyl acetate (50 mL). This solution was washed with 20 mL each of 0.5 M HCl and water, dried over Na_2SO_4, and evaporated to leave 74 mg (79%) of **1** as a white solid; mp 105−107 °C (lit.[7] 105−108 °C); $[\alpha]_D^{25}$ 57.2 (*c* 0.51, $CHCl_3$) [lit.[7] 58.06 (*c* 0.47, $CHCl_3$)].

Agglomerin C (2c). A solution of 3-dodecanoyl-5-hydroxymethyl-[5*H*]furan-2,4-dione **11c** (62 mg, 0.2 mmol) in dry THF (1 mL) was treated with DMAP (10 mg), methanesulfonyl chloride (0.031 mL, 0.4 mmol), and NEt_3 (0.11 mL, 0.8 mmol), and the resulting mixture was stirred at room temperature for 5 h. The mixture was then poured into ice−water and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, and concentrated. The resulting pale yellow crude product was dissolved in THF (12 mL); 0.1 M aqueous NaOH (6 mL) was added, and the mixture was stirred at room temperature for 3 days and finally acidified with 1 M HCl to pH 1. The mixture was extracted with ethyl acetate, which was then washed with brine, dried, and concentrated. The residue was purified by CC on silica gel to leave white solid **2c** (45 mg, 76%): mp 125−127 °C (lit.[12] 125−128 °C); R_f 0.34 ($CHCl_3$/MeOH 10:1); ν_{max} (ATR)/cm^{-1} 3355 (br), 2922, 1723, 1620, 1467; ^{1}H NMR (300 MHz, CD_3OD) δ 0.88 (t, J = 6.9 Hz, 3 H), 1.21−1.42 (m, 16 H), 1.50−1.63 (m, 2 H), 2.78 (t, J = 6.9 Hz, 2 H), 4.83 (s, 1 H), 5.13 (s, 1 H); *m/z* (EI) 294 (10) [M$^+$], 277 (5),

167 (10), 154 (25), 139 (10), 98 (10), 84 (10), 71 (20), 55 (35), 41 (100). HR-MS: Found 294.18310. Calcd for $C_{17}H_{26}O_4$ 294.18311.

Immobilized (2*R*)-2-Hydroxy-3-triphenylmethoxypropanoic Acid β-Trimethylsilylethyl Ester (15). Trityl chloride polystyrene resin (0.5 g, 0.85 mmol; Fluka, 100−200 mesh, 1% DVB, loading 1.7 mmol/g) was suspended in dry CH_2Cl_2 (10 mL) and allowed to swell for 10 min. The solvent was removed by filtration; the resin was resuspended in fresh CH_2Cl_2 (7 mL) and treated with crude **14** (230 mg, 1.25 mmol) and NEt_3 (0.18 mL, 1.25 mmol). The mixture was gently shaken at room temperature for 6 h and then filtered. The resin was washed with 2 × 10 mL each of CH_2Cl_2, DMF, MeCN, THF, MeOH, toluene, and THF and finally dried on an oil pump; ν_{max} (ATR)/cm^{-1} 3407, 1734, 1249, 857, 835.

Immobilized (5*R*)-4-Trimethylsilylethoxy-5-(triphenylmethoxy)methyl-[2*H*]furan-2-one (16). Under a blanket of dry argon, **15** (640 mg, 0.85 mmol) was suspended in anhydrous THF (8 mL) and treated with Ph_3PCCO (367 mg, 1.25 mmol) and benzoic acid (10 mg). The mixture was gently shaken at 60 °C for 12 h. The resin was collected on a sintered frit, washed in turn with 2 × 20 mL each of THF, DMF, MeCN, THF, MeOH, toluene, and THF, and dried in a vacuum. Completion was ascertained by the weight increase and the disappearance of the OH band of **15** in the IR spectra; ν_{max} (ATR)/cm^{-1} 1740, 1631, 1249, 857, 835.

Immobilized (5*R*)-5-(Triphenylmethoxy)methyl-[2*H*]furan-2,4-dione (17). Resin **16** (660 mg, 0.85 mmol) was suspended in dry THF (7 mL), treated with TBAF·$3H_2O$ (800 mg, 2.5 mmol), and gently shaken at room temperature for 3 h. Water (2 mL) was added, and shaking was continued for an additional 20 min. The resin was then collected on a sintered frit, washed in turn with 2 × 20 mL each of CH_2Cl_2, DMF, MeCN, THF, MeOH, toluene, and THF, and dried in vacuo; ν_{max} (ATR)/cm^{-1} 1727, 1599.

Immobilized (5*R*)-3-Hexadecanoyl-5-(triphenylmethoxy)-methyl-[2*H*]furan-2,4-dione (18). Resin **17** (560 mg, 0.85 mmol) was suspended in anhydrous CH_2Cl_2 (7 mL), treated with NEt_3 (0.14 mL, 1.0 mmol), DMAP (20 mg), palmitic acid (256 mg, 1.0 mmol), and DCC (226 mg, 1.1 mmol), and the resulting mixture was gently shaken at room temperature for 16 h. The resin was filtered and washed with 2 × 20 mL each of CH_2Cl_2, DMF, MeCN, THF, MeOH, toluene, and THF; ν_{max} (ATR)/cm^{-1} 1725, 1641.

(5*R*)-RK-682 (1). Resin **18** (700 mg, 0.85 mmol) was suspended in anhydrous CH_2Cl_2 (10 mL), swollen for 10 min, filtered, and then resuspended in 8 mL of the cleaving mixture (CH_2Cl_2/TFA/Et_3SiH 90:5:5, v/v/v) whereupon the initially yellow color of the resin turned red. The mixture was shaken at room temperature for 20 min and filtered, and the resin was washed with 10 mL each of CH_2Cl_2, THF, MeOH, and toluene. The combined filtrates were evaporated to dryness, yielding pure (5*R*)-RK-682 (80 mg, 26% yield calcd on the basis of **14**).

Acknowledgment. This paper is dedicated to Professor Steven V. Ley on the occasion of his 60th birthday. Financial support from the Deutsche Forschungsgemeinschaft (Grant Scho 402/7-2) is gratefully acknowledged. We thank Miriam Siebenbürger and Paul Majkut for practical contributions during their third year's projects.

Supporting Information Available: Syntheses and characterizations of pure compounds **4**, **6**, **10**, **11**, and **13**, spectroscopic/analytical data of pure known compounds **1**, **2a**, **2b**, and **9**, as well as experimental procedures for crude compounds **5** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050797I