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First enantiospecific Baker–Venkataraman-rearrangements aiming at the total synthesis of chiral anthrapyran antibiotics

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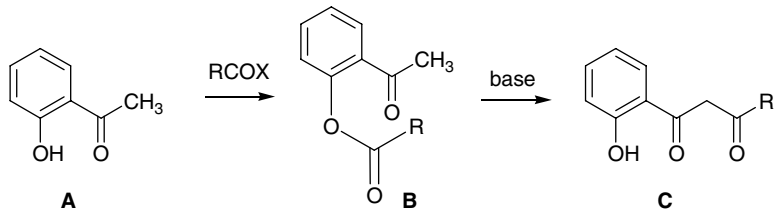
Abstract—The base-catalyzed acyl transfer (Baker–Venkataraman reaction) of chiral 2-acetyl-1-hydroxyanthraquionone esters **6** of 2-methylbutanoic acid or **11** of *O*-allyl lactic acid proceeds with virtually no racemization to ketides **7** and **12**. The subsequent acid-catalyzed cyclization to the chiral anthra[1,2-*b*]pyran antibiotics such as (*S*)-1″-11-dideoxyespicufolin **8** or **13** also occurs with a very low racemization.

1. Introduction

The Baker–Venkataraman reaction is known as the intramolecular acyl transfer of phenol esters **B** to an acyl group of the type shown in Scheme 1. Esters **B** can easily be prepared from *ortho*-acyl phenols **A** to yield β-diketo chain elongation products **C** upon treatment with the base. The intramolecular ester condensation facilitates the acyl transfer and yields of **C** are generally good with conditions comparatively mild. This method was used for the preparation of chromones,[1,2] coumarines,[3,4] and benzindenopyrandiones.[5] The scope in the choice of residue R on the ester is broad and it can be aliphatic, olefinic, aromatic, or heteroaromatic, as investigated by Kraus et al.[6]

The construction of β-diketo side chains on an aromatic or quinoide nucleus is ideally suited for the synthesis of aromatic polyketide derived natural products and was used in the biomimetic-type synthesis of anthracylines[7] and angucyclines[8] (review[9]). Similarly, the Baker–Venkataraman reaction was employed in the synthesis of a large group of anthrapyran antibiotics.[10–12] In this connection it was of interest that in contrast to normal phenolic esters[13] the intermolecular C-acylation was not possible with acylated anthraquinone precursors (only O-acylation was observed[14]), whereas the intramolecular version gave good results in the C–C coupling products and was the only option for the ketide C–C chain elongation with quinoide substrates.[12] However, to the best of our knowledge, no



Scheme 1. General scheme of the Baker–Venkataraman reaction.

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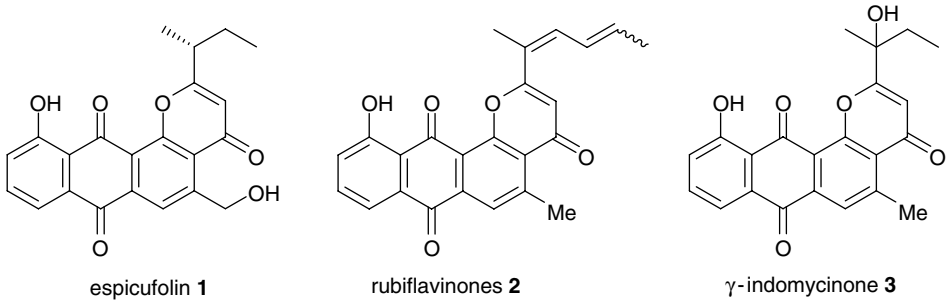


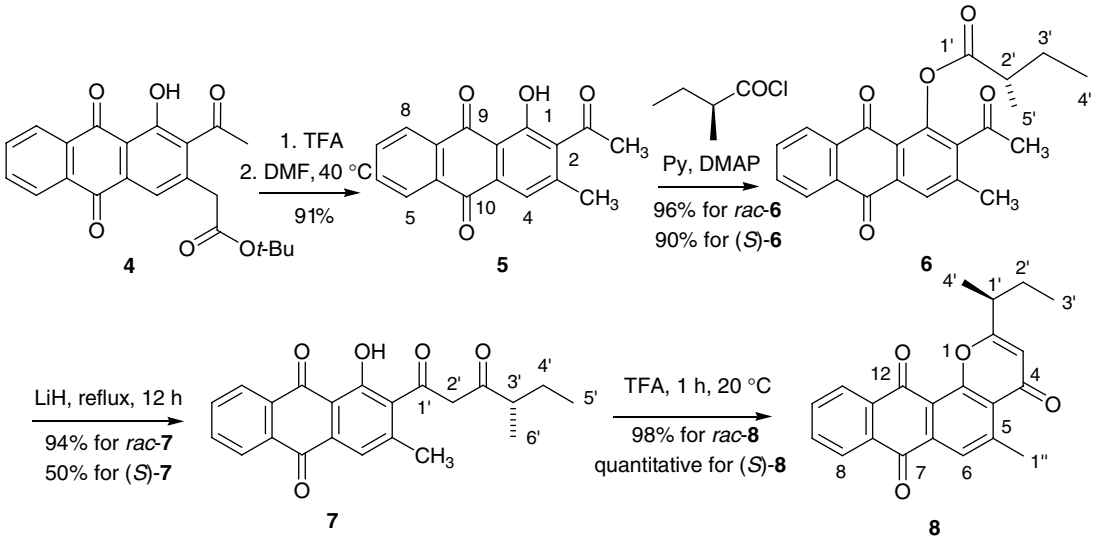
Figure 1. Representative chiral or functionalized anthra[1,2-*b*]pyranones.

examples of enantioselective acyl transfer reactions with homochiral or α-oxygenated esters **B** under Baker–Venkataraman conditions are known. In fact, the relatively strong bases used for the transformation of **B** to **C** seemed to exclude such a reaction without causing considerable racemization.

The long known class of anthra[1,2-*b*]pyran antibiotics (reviews[15,16]) have gained new interest as a tool in molecular biochemistry,[17] in particular due to their specific DNA intercalation and alkylation.[18–21] In addition, some representatives show interesting biological properties such as the new antitherpeutic agent, AH-1763 IIa, produced by the *Streptomyces cyaneus* strain[22] and recently prepared by synthesis,[23] or the novel neuronal cell protecting espicufolin **1**, produced by a *Streptomyces* sp.[24] Another large group are rubiflavinones **2**[25–27] with an hexadiene side chain on C-2 or γ-indomycinone **3** with a butanol side chain at C-2,[28] with a tertiary hydroxy group in the C-4 side chain. Herein we report for the first time on Baker–Venkataraman reactions which occurred with virtually no racemization during base-catalyzed acyl transfer, extending the scope of the reaction considerably, for instance, for the synthesis of chiral or complex anthrapyran antibiotics as shown in Figure 1.

2. Results and discussion

The reaction sequence leading to 2-butenylanthra[1,2-*b*]-pyran **8** was performed with the racemic 2-methylbutanoic acid and in parallel using the commercially available (*S*)-2-methylbutanoic acid as the chiral acid component in the first enantioselective Baker–Venkataraman reaction (Scheme 2). The starting anthraquinone **5** was produced from the known *tert*-butyl ester **4**[7] by acid-catalyzed ester cleavage followed by decarboxylation in dry DMF (Scheme 2). Our initial attempts for the decarboxylation of the intermediate anthraquinone acid in normal DMF solution were very sluggish even at elevated temperatures. We then discovered that the addition of molecular sieves accelerated considerably the decarboxylation reaction even at a much lower temperature (40 °C). This rate increase by using rigorously dried DMF was reproducible and also applicable for a number of related esters. We presume that the presence of trace amounts of water may stabilize the carboxylic acid by intra or intermolecular chelate formation. This accelerated reaction under anhydrous conditions may prove to be a generally useful modification for the decarboxylation of β-keto acids and related phenylogous or vinylogous substrates.



Scheme 2. Enantiospecific Baker–Venkataraman reaction of (*S*)-**6** to (*S*)-**7** and cyclization to (*S*)-1″-11-dideoxyespicufolin **8**.

Having phenolic anthraquinones **5** in hand, acylation with *rac*-2-methylbutanoyl chloride and (*S*)-2-methylbutanoyl chloride, prepared by oxalyl chloride treatment of the corresponding commercially available acids, was studied next. The steric hindrance and reduced reactivity of the chelated phenolic hydroxyl group was overcome by the addition of 4-dimethylaminopyridine (DMAP)[29] and esters *rac*-**6** and (*S*)-**6** were isolated in 96% and 90% yield, respectively (Scheme 2). The crucial next step was the lithium hydride mediated Baker–Venkataraman reaction of *rac*-**6** and (*S*)-**6** to β-diketo-anthraquinone *rac*-**7** and (*S*)-**7**. The NMR spectra of the β-diketo compounds indicated that they existed predominantly in the enol tautomeric form (see Section 4). In the cases of the achiral or racemic substrates, the reactions were usually performed under reflux[12] and the respective rearrangement products were isolated in 94% and 50%, respectively. It was observed that in the case of smaller scale reactions, the yields were generally lower due to partial saponification of esters **6** by traces of water to phenol **5**, which could be recovered in 35% yield.

The final step in the synthetic protocol was the cyclization of *ortho*-phenols *rac*-**7** and (*S*)-**7** to *rac*-**8** and (*S*)-**8**. As found in a previous investigation,[12] the simple dissolution of the open chain precursors for a short time in trifluoroacetic acid was the method of choice for this crucial cyclization step and *rac*-**8** and (*S*)-**8** were isolated in nearly quantitative yields in both cases.

It is noteworthy that none of the products starting from enantiomerically pure chiral (*S*)-2-methylbutanoic acid showed any detectable optical activity. In fact, the specific rotation of (*S*)-2-methylbutanoic acid itself was very low (+19, neat; Acros Organics, 19.8 1.15 g/100 mL $CHCl_3$) and the near optical inactivity of the anthraquinone-linked derivatives **7** and **8** was thus not that surprising. Fortunately however, the enantiomers of *rac*-**7** and *rac*-**8** could be separated by chiral HPLC (see Section 4 for conditions) and the results are shown in Figure 2. Both racemic compounds **7** and **8** showed a clear baseline separation. Thus, in spite of the use of basic reaction conditions, the crude Baker–Venkataraman product **7** had greater than 99% enantiomeric excess. We believe that the reason for this surprising result is due to the much higher C–H acidity of the conjugated acyl group at C-2 than that of the ester α-C–H acidity, which would lead to racemization. Additionally, the resistance of product **7** to racemization under the basic reaction conditions may be due to the formation of the very stable enolate or phenolic anion of the phenolic β-diketo compound. The activation energy for a second deprotonation of this species may be too high for the comparatively mild conditions employed. The next cyclization step could also be performed without any significant racemization and the crude 2-butenyl-anthra[1,2-*b*]pyran *rac*-**8** showed ee >97%. In fact, as shown by the minor amount of racemization, this acid-catalyzed reaction seemed to be even more prone to epimerization than the previous base-catalyzed acyl transfer. In future work, the minimum time in the acidic medium required for the induction of cyclization should be optimized in order to minimize racemization. The enantiomerically enriched (>97% ee) anthra[1,2-*b*]pyran **8** is a close derivative of neuroprotective espicufolin **1**[24] and can be named as (*S*)-1″-11-dideoxyespicufolin **8**. Derivative (*S*)-**8** is enantiomeric to the natural product **1** as determined by the total synthesis of the enantiomeric (*R*)-configured natural product[30,31] and its biological activity is presently under investigation.

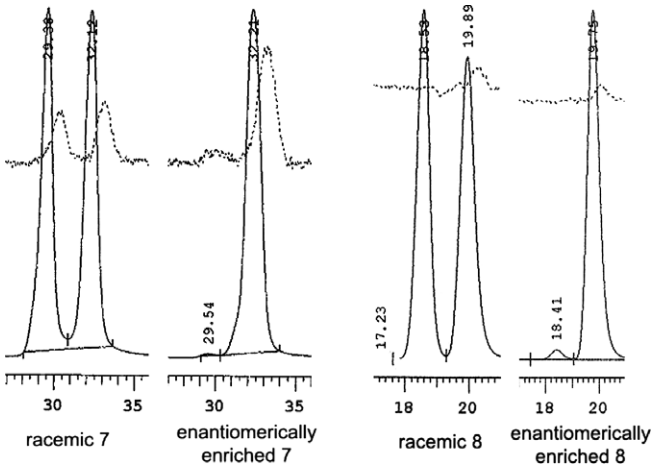
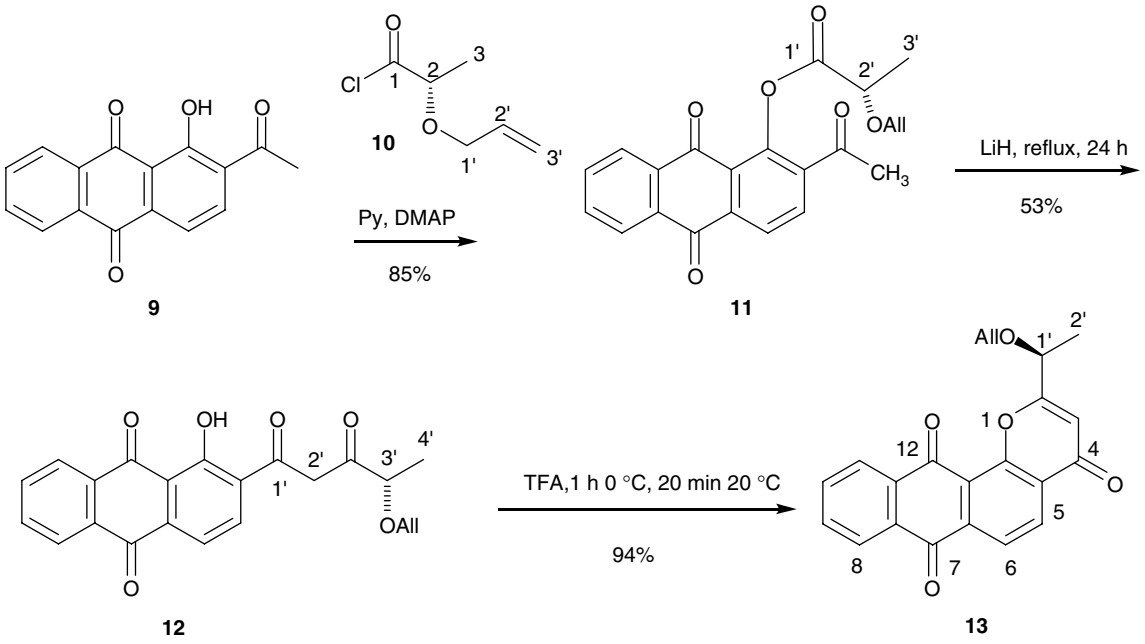


Figure 2. HPLC diagrams of crude reactions products of the Baker–Venkataraman reaction of **6** to **7** and acid-catalyzed cyclization of **7** to **8**.

In the second part of this work, we investigated the Baker–Venkataraman reaction of the racemic and enantiomerically pure *O*-allyl-lactic ester *rac*-**11** and **11** to ketides *rac*-**12** and **12** and their cyclization to anthrapyranes *rac*-**13** and **13** (Scheme 3, yields given for enantiomerically enriched compounds were similar as for the racemic compounds). This model reaction would not only open the way to enantiomerically pure 1′-hydroxy-anthrapyranones of the indomycinone type (see Fig. 1), but also give 1′-functionalized derivatives for an easy chain elongation to rubiflavinones **2** (Fig. 1), pluramycines, or hedamycines.[15]

For the starting material, we selected the simple 2-acetyl-1-hydroxy-9,10-anthraquinone **9**, easily available by Marschalk reaction with 1-hydroxy-9,10-anthraquinone and acetaldehyde, followed by the oxidation of the hydroxymethyl intermediate to **9**.[12] Esterification with *O*-allyl lactic acid chloride **10** to ester **11** proceeded smoothly and in a good yield (85%) in spite of the sterically hindered ester component. The Baker–Venkataraman rearrangement of ester **11** gave 53% of β-diketoalky-anthraquinone **12**, together with 40% of the saponified anthraquinones **9** that could be recycled. Finally, β-diketoalky phenol **12** was cyclized in an excellent yield (94%) to 2-allyloxy-substituted anthrapyranon **13**, without cleavage or isomerization of the allyl protecting group.

In contrast to isobutyl-substituted derivatives **7** and **8**, 1′-oxygenated products **12** and **13** showed noticeable levorotational specific rotation (−88 and −87, respectively). Since no comparison compounds for specific rotation were available, the ee values were again determined by chiral HPLC. Ester **11** was found to have a 90% ee and anthrapyrane **13** an 85% ee, accounting for ca. 2.5% of racemization over the two steps from **11** to **13**.



Scheme 3. Incorporation of optically active *O*-allyl lactate **11** into a Baker–Venkataraman reaction to **12** and cyclization to anthrapyrane **13**.

3. Conclusion

In conclusion, we have shown for the first time that the base-catalyzed intramolecular acyl migration (Baker–Venkataraman rearrangement) with chiral 2-alkyl or 2-allyoxy phenolic esters (e.g., **6** or **11**) proceeds without noticeable racemization to anthraquinones **7** and **12** with chiral ketide side chains. The racemization observed in the subsequent acid-catalyzed cyclization to anthrapyranones **8** and **13**, respectively, was the very most 3%. This opens the way for the synthesis of enantiomerically pure anthrapyran antibiotics using the Baker–Venkataraman rearrangement of 2-acylanthraquinone esters. In addition, the oxygen function introduced by the rearrangement of *O*-ally lactic esters, namely, **11** allows the elaboration of more complex side chains at C-2 of the anthrapyran skeleton.

4. Experimental

For general methods and instrumentation see reference.[32] Conditions for HPLC analysis: column type: Chiralcel AD-H; detector type: UV (operated at 254 nm); pump Merck-Hitachi L-7100; solvent: hexane/isopropanol 50:50; volume injected: 20 μL; flow rate: 0.3 mL/min; detection at 254 nm. GC analysis: HP-5890, Integrator Merck-Hitachi D-2000. FS-Hydrodex-beta-3P column. Init. temp 80 °C, init. time 5 min, rate 0.5 °C/min, final temp 150 °C.

4.1. 2-Acetyl-1-hydroxy-3-methylanthracene-9,10-dione 5

Trifluoroacetic acid (3 mL) was added to a solution of *tert*-butyl 2-(3-acetyl-4-hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl)acetic acid **4**[7] (2.33 g, 6.13 mmol) in dry CH_2Cl_2 (30 mL) and stirred at reflux for 1 h. Dichloromethane (15 mL) was then added and the solvent was removed under reduced pressure. The procedure was repeated twice to remove the trace amounts of trifluoroacetic acid. The residue was then purified by crystallization from ethanol to afford the intermediate acid of ester **5** as light yellow crystals (1.91 g, 5.88 mmol, 96%, mp 211 °C). For decarboxylation, dry DMF (5 mL) and powdered 3 Å molecular sieves (2 g) were added to the acid (1.87 g, 5.77 mmol) and the reaction mixture was stirred over night under nitrogen at 40 °C. Ethyl acetate (200 mL) was added and the organic phase was washed successively with HCl (2 mol/L, 2×60 mL), saturated $NaHCO_3$ solution (2×50 mL), water (60 mL), and brine (60 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by crystallization from ethanol to afford methyl anthraquinone as orange crystals (1.53 g, 5.47 mmol, 95%, mp 207 °C). IR (KBr) 3438, 1695, 1676, 1639, 1591, 1556, 1475, 1442, 1388, 1354, 1290, 1275, 1259, 1238, 1209, 1132, 1045, 976 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H, CH_3), 2.64 (s, 3H, $CH_{3,CO}$), 7.69 (s, 1H, 1″-H), 7.83–7.86 (m, 2H, 6″-H, 7″-H), 8.30–8.33 (m, 2H, 5″-H, 8″-H), 12.94 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3 (q, CH_3), 31.9 (q, $CH_{3,CO}$), 114.4 (s, C-9), 121.7 (d, C-4), 126.9 (d, C-5/C-8), 127.5 (d, C-5/C-8), 133.0 (s), 133.2 (s,), 133.5 (s), 134.3 (d, C-6/C-7), 134.8 (d, C-6/C-7), 135.9 (s), 145.0 (s), 159.7 (s, C-1), 182.1 (s, C-10), 188.2 (s, C-9), 202.9 (s, CO); MS (EI, 70 eV, 200 °C) 280 (50) [M^+], 265 (100), 181 (10), 167 (28), 149 (78), 113 (5), 83 (5), 71 (14), 69 (18), 57 (18); HRMS (EI, 70 eV) $C_{17}H_{12}O_4$ calcd for 280.07356. Found 280.07345. Anal. Calcd for $C_{17}H_{12}O_4$ (280.27) 72.85; H, 4.32. Found: C, 72.75; H, 3.79.

4.2. 2-Acetyl-3-methyl-9,10-dioxo-9,10-dihydroanthracen-1-yl 2-methylbutanoate 6

A solution of phenol **5** (315 mg, 1.13 mmol) in dry dichloromethane (10 mL) was treated at 0 °C successively with

pyridine (0.2 mL, 2.25 mmol), *rac*-2-methylbutanoyl chloride (prepared from 2-methylbutanoic acid and oxalyl chloride) (0.2 mL, 2.25 mmol) and DMAP (3 mol %). The mixture was stirred for 6 h at 20 °C (TLC monitoring). Water was then added (50 mL) and the aqueous phase extracted with dichloromethane (2 × 50 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL), diluted HCl (2 mol/L, 20 mL), water (20 mL), and brine (30 mL). The solution was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by crystallization (diethyl ether) to give the ester **6** as yellow crystals (398 mg, 1.09 mmol, 96%, mp 152 °C). The reaction with the corresponding (*S*)-2-methylbutanoyl chloride (263 mg, 2.18 mmol), 169 mg (0.60 mmol) of phenol **5** yielded 195 mg (0.54 mmol, 90%) of (*S*)-**6**. IR (KBr) 2972, 2935, 2879, 1770, 1711, 1674, 1589, 1462, 1354, 1333, 1282, 1252, 1209, 1163, 1132, 1107, 1090, 798, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, $J_{3',4'} = 7.5$ Hz, 3H, 4″-H), 1.41 (d, $J_{2',5'} = 7.0$ Hz, 3H, 5″-H), 1.67 (m, 1H, $3'_\alpha$-H), 2.00 (m, 1H, $3'_\beta$-H), 2.45 (s, 3H, $COCH_3$), 2.53 (s, 3H, CH_3), 2.86 (m, 1H, 2″-H), 7.71–7.81 (m, 2H, 6-H, 7-H), 8.13 (s, 1H, 4-H), 8.22–8.28 (m, 2H, 5-H, 8-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5 (q, C-4″), 15.8 (q, C-5″), 19.5 (q, C-1‴), 26.1 (t, C-3″), 31.8 (q, C-2″), 41.0 (d, C-2″), 123.2 (s, C-9a), 126.9 (d, C-7), 127.2 (d, C-5), 127.3 (d, C-4), 132.6 (s, C-8a), 133.9 (d, C-6), 134.2 (s, C-10a), 134.4 (d, C-8), 134.6 (s, C-4a), 141.5 (s, C-2), 142.2 (s, C-3), 146.5 (s, C-1), 174.2 (s, C-1″), 181.1 (s, C-9), 182.3 (s, C-10), 202.0 (s, C-1″); MS (EI, 70 eV, 200 °C) 364 (15) [M^+], 280 (50), 265 (100), 209 (5), 181 (15), 167 (22), 149 (42), 111 (32), 97 (38), 85 (54), 72 (44), 57 (88); HRMS (EI, 70 eV) $C_{22}H_{20}O_5$ calcd for 364.13107. Found: 364.13102. Anal. Calcd for $C_{22}H_{20}O_5$ (364.39) C, 72.51; H, 5.53. Found: C, 71.72; H, 5.27.

4.3. 1-Hydroxy-3-methyl-2-(4-methyl-3-oxohexanoyl)-anthracene-9,10-dione 7

A solution of phenol ester **6** (368 mg, 1.00 mmol) in THF (50 mL) was treated at 0 °C with LiH (10 mmol, 80 mg) and the suspension was stirred at 40 °C overnight (TLC monitoring). The mixture was carefully neutralized at 0 °C by the slow addition of HCl (2 mol/L, 2 mL), reduced to one fifth of its volume under reduced pressure, and diluted with dichloromethane (100 mL). The organic phase was washed successively with HCl (2 mol/L, 2 × 40 mL) and water (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford diketone **7** (341 mg, 0.94 mmol, 94%, mp 140 °C) as yellow crystals after crystallization from dichloromethane/ethanol (1:1). A similar conversion of (*S*)-**6** (111 mg, 0.30 mmol), yielded (*S*)-**7** (55 mg, 0.15 mmol), 50% in addition to 34 mg of anthraquinone **5** (35%). IR (KBr) 3440, 2966, 2931, 2875, 1674, 1626, 1591,1481, 1446, 1360, 1282, 1273, 1130, 970, 783, 715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (for enol tautomer) 1.00 (t, $J_{5',6'} = 7.5$ Hz, 3H, 6″-H), 1.23 (d, $J_{4',7'} = 7.1$ Hz, 3H, 7″-H), 1.57 (m, 1H, $5'_\alpha$-H), 1.76 (m, 1H, $5'_\beta$-H), 2.42 (m, 1H, 4″-H), 2.51 (s, 3H, CH_3), 5.89 (s, 1H, 2″-H), 7.72 (s, 1H, 4-H), 7.86–7.90 (m, 2H, 6-H, 7-H), 8.29–8.36 (m, 2H, 5-H, 8-H), 13.00 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (for enol tautomer) 11.4 (q, C-6″), 16.7 (q, C-7″), 20.4 (q, C-1″), 27.1 (t, C-5″, CH_2), 44.1 (d, C-4″), 101.9 (d, C-2″), 114.4 (s, C-9a), 121.2 (d, C-7), 126.8 (d, C-5), 127.2 (d, C-4), 132.0 (s, C-8a), 133.1 (s, C-2), 133.2 (s, C-4a), 133.5 (s, C-10a), 134.3 (d, C-6), 134.8 (d, C-8), 146.5 (s, C-3), 159.9 (s, C-1), 182.0 (s, C-10), 185.1 (s, C-1″), 188.3 (s, C-9), 199.0 (s, C-3″); MS (EI, 70 eV, 200 °C) 364 (22) [M^+], 349 (45), 307 (28), 280 (55), 265 (100), 238 (5), 181 (12), 152 (15), 85 (4), 57 (15); HRMS (EI, 70 eV) $C_{22}H_{20}O_5$: calcd for 364.13107. Found: 364.13231. Anal. Calcd for $C_{22}H_{20}O_5$ (364.39) C, 72.51; H, 5.53. Found: C, 72.27; H, 4.97.

4.4. 2-*sec*-Butyl-5-methyl-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione 9 ent-(1″,11-dideoxy-espicufolin)

Trifluoroacetic acid (5 mL) was added to diketone **7** (148 mg, 0.41 mmol) and the solution stirred at room temperature for 1 h. Dichloromethane (15 mL) was then added and the solvent was removed under reduced pressure. The procedure was repeated twice to remove trifluoroacetic acid. The crude product was dissolved in dichloromethane (50 mL), successively washed with saturated $NaHCO_3$ solution (20 mL), diluted HCl (2 mol/L, 20 mL), water (20 L), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Crystallization (toluene/ethanol) afforded the product as yellow crystals (138 mg, 0.40 mmol, 98%, mp 184 °C). A related cyclization of (*S*)-**7** (10 mg, 0.027 mmol) afforded 10 mg of (*S*)-**8** (quantitative). IR (KBr) 2968, 2933, 2875, 1680, 1649, 1585, 1460, 1442, 1385, 1369, 1311, 1277, 1107, 935, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, $J_{2',3'} = 7.5$ Hz, 3H, 3″-H), 1.47 (d, $J_{1',4'} = 6.9$ Hz, 3H, 4″-H), 1.83 (m, 1H, $2'_\alpha$-H), 2.01 (m, 1H, $2'_\beta$-H), 2.77 (m, 1H, 1″-H), 3.05 (s, 3H, CH_3), 6.29 (s, 1H, 3-H), 7.81–7.86 (m, 2H, 9-H, 10-H), 8.09 (s, 1H, 6-H), 8.30–8.35 (m, 2H, 8-H, 11-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5 (q, C-3″), 17.7 (q, C-4″), 23.9 (q, CH_3), 27.3 (t, C-2″), 40.4 (d, C-1″), 110.8 (d, C-3), 120.4 (s, C-12a), 125.3 (d, C-10), 126.1 (s, C-11a), 126.8 (d, C-8), 127.3 (d, C-6), 132.2 (s, C-4a), 133.7 (d, C-9), 134.6 (s, C-7a), 134.7 (d, C-11), 136.0 (s, C-6a), 148.7 (s, C-5), 156.5 (s, C-12b), 173.8 (s, C-2), 180.3 (s, C-12), 180.7 (s, C-4), 182.6 (s, C-7); MS (EI, 70 eV, 200 °C) 346 (18) [M^+], 318 (5), 279 (18), 265 (32), 224 (15), 196 (15), 181 (10), 167 (42), 149 (88), 135 (15), 125 (35), 113 (16), 97 (40), 83 (30), 69 (64), 57 (15), 43 (100); HRMS (EI, 70 eV) $C_{22}H_{18}O_4$: calcd for 346.12051. Found: 346.12051.

4.5. (*S*)-2-Allyloxy lactic acid[33]

A solution of ethyl L-(−)-lactate (1.0 mL, 17.6 mmol), silver oxide (4.0 g, 17.6 mmol), and allyl bromide (6 mL) in dry acetone (40 mL) was refluxed for 1 h. After filtration over Celite®, the solvents were concentrated under reduced pressure to give 3.1 g of crude product which was used in the next step without further purification. Purification of 250 mg of the crude product by flash chromatography (petroleum ether/ethyl acetate 9/1) afforded ethyl (*S*)-2-allyloxypropanoate (186 mg) as a colorless oil. The product was enantiomerically pure as analyzed by chiral GC: (retention times for racemate: 64.8 and 65.6 min, retention time for enantiomerically pure sample: 64.8 min).

$[\alpha]_D^{20} = -69$ (*c* 1.05, $CHCl_3$) [Ref. 33: −64.2 (*c* 2.7, methanol)]. ^1H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, $J_{2'',1''} = 7.1$ Hz, 3H, 2-H″), 1.38 (d, $J_{3,2} = 6.9$ Hz, 3H, 3-H), 3.91 (ddt, $J_{1',1'} = 12.5$ Hz, $J_{1',2'} = 6.0$ Hz, $J_{1',3'} = 1.4$ Hz, 1H, 1-H′), 3.97 (q, $J_{2,3} = 6.9$ Hz, 1H, 2-H), 4.11 (ddt, $J_{1',1'} = 12.5$ Hz, $J_{1',2'} = 5.5$ Hz, $J_{1',3'} = 1.4$ Hz, 1H, 1″-H), 4.18 (q, $J_{1'',2''} = 7.1$ Hz, 2H, 1-H″), 5.16 (ddt, $J_{3',2'} = 10.4$ Hz, $J_{3',3'} = J_{3',1'} = 1.4$ Hz, 1H, 3-H′), 5.26 (ddt, $J_{3',2'} = 17.2$ Hz, $J_{3',3'} = J_{3',1'} = 1.6$ Hz, 1H, 3-H′), 5.89 (dddd, $J_{2',3'trans} = 17.2$ Hz, $J_{2',3'cis} = 10.4$ Hz, $J_{2',1'} = 6.0$ Hz, $J_{2',1'} = 5.5$ Hz, 1H, 2-H′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2 (q, C-2″), 18.6 (q, C-3), 60.7 (t, C-1″), 71.0 (t, C-1″), 74.0 (d, C-2), 117.6 (t, C-3″), 134.1 (d, C-2″), 173.2 (s, C-1).

For saponification of ethyl ester, 0.2 mol/L solution of lithium hydroxide (177 mL) was added dropwise to a solution of ethyl (*S*)-2-allyloxypropanoate (2.8 g, 17.7 mmol) in THF (170 mL), at 0 °C over a period of 20 min. The mixture was stirred for 3 h at room temperature and concentrated to one-half of the volume under reduced pressure. After acidification with diluted hydrochloric acid (2 mol/L), the mixture was extracted three times with ethyl acetate, the combined organic phases were dried over anhydrous sodium sulfate, and the solvents were concentrated under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate/acetic acid 90/10/1 to 80/20/1) afforded (*S*)-2-allyloxypropanoic acid (1.9 g, 82% yield) as a colorless oil. $[\alpha]_D^{20} = -57.5$ (*c* 1.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, $J_{3,2} = 6.9$ Hz, 3H, 3-H), 3.98 (ddt, $J_{1',1'} = 12.5$ Hz, $J_{1'-2'} = 6.1$ Hz, $J_{1'-3'} = 1.3$ Hz, 1H, 1-H′), 4.05 (q, $J_{2,3} = 6.9$ Hz, 1H, 2-H), 4.15 (ddt, $J_{1',1'} = 12.5$ Hz, $J_{1',2'} = 5.6$ Hz, $J_{1',3'} = 1.4$ Hz, 1H, 1-H′), 5.20 (ddt, $J_{3',2'} = 10.4$ Hz, $J_{3',1'} = 1.3$ Hz, $J_{3',3'} = 1.3$ Hz, 1H, 3-H′), 5.28 (dtd, $J_{3',2'} = 17.0$ Hz, $J_{3',1'} = 1.7$ Hz, $J_{3',3'} = 1.6$ Hz, 1H, 3-H′), 5.90 (ddt, $J_{2',3'trans} = 17.3$ Hz, $J_{2',3'cis} = 10.7$ Hz, $J_{2',1'} = 5.7$ Hz, 1H, 2-H′), 7.91 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 18.3 (q, C-3), 71.1 (t, C-1″), 72.5 (d, C-2), 118.1 (t, C-3″), 133.7 (d, C-2″), 178.1 (s, C-1).

4.5.1. (*S*)-2-(Allyloxy)propanoyl chloride 10. Oxalyl chloride (0.2 mL, 2.2 mmol) was added at 20 °C under argon to a solution of (*S*)-2-allyloxypropanoic acid (200 mg, 1.5 mmol) in dry dichloromethane and the mixture was stirred for 2 h. After dilution with dichloromethane, the solvent was removed at reduced pressure to afford (*S*)-2-(allyloxy)propanoyl chloride (219 mg, 98% yield), which was used without further purification.

4.6. (*S*)-2-Acetyl-9,10-dihydro-9,10-dioxoanthracen-1-yl 2-(allyloxy)propanoate 11

(*S*)-2-(Allyloxy)propanoyl chloride **10** and DMAP (5 mg) were added at room temperature under argon to a solution of 2-acetyl-1-hydroxyanthraquinone **9**[12] (271 mg, 1.0 mmol) in dry dichloromethane (3.4 mL) and dry pyridine (1 mL). After stirring for 4 h, the reaction was quenched by the addition of water. The mixture was extracted with dichloromethane, and the combined organic phases were washed with saturated sodium hydrogencarbonate, dilute hydrochloric acid, and brine, and dried over anhydrous sodium sulfate. The solvents were removed under reduced pressure. Purification of the residue by flash chromatography (dichloromethane/methanol 100/0 to 98/2) afforded ester **11** (328 mg, 85%) as a yellow solid and anthraquinone **9** (35 mg, 13% recovered starting material), mp 64–66 °C. $[\alpha]_D^{20} = -16$ (*c* 1.03, $CHCl_3$); UV (MeOH): λ_{max} ($\log\varepsilon$) 205 nm (4.85), 251 (4.50), 383 (3.92); IR (KBr) 1769, 1700, 1686, 1588, 1318, 1257, 1217, 1124, 1114, 714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, $J_{3,2} = 7.0$ Hz, 3H, 3-H), 2.63 (s, 3H, 2-H″), 4.26 (ddt, $J_{gem} = 12.6$ Hz, $J_{1''',2'''} = 6.2$ Hz, $J_{1''',3'''} = 1.3$ Hz, 1H, 1-H‴), 4.43 (ddt, $J_{gem} = 12.6$ Hz, $J_{1''',2'''} = 5.2$ Hz, $J_{1''',3'''} = 1.5$ Hz, 1H, 1-H‴), 4.6M (q, $J = 7.0$ Hz, 2H, 2-H), 5.27 (m, 1H, 3-H‴), 5.44 (ddt, $J_{3''',2'''} = 17.2$ Hz, $J_{gem} = J_{3''',1'''} = 1.7$ Hz, 1H, 3-H‴), 6.02 (dddd, $J_{2''',3'''} = 17.2$ Hz, $J_{2''',3'''} = 10.4$ Hz, $J_{2''',1'''} = 6.2$ Hz, $J_{2''',1'''} = 5.2$ Hz, 1H, 2-H‴), 7.81 (m, 2H, 6-H′, 7-H′), 8.05 (d, $J_{3'-4'} = 8.1$ Hz, 1H, 3-H′), 8.22, 8.27 (2 * m, 2 * 1H, 5-H′, 8-H′), 8.34 (d, $J_{4',3'} = 8.0$ Hz, 1H, 4-H′); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2 (q, C-3), 30.4 (q, C-2″), 71.4 (t, C-1‴), 74.0 (d, C-2), 117.8 (t, C-3″), 125.6 (d, C-4″), 125.7 (q, C-9″a), 127.1, 127.5 (2 * d, C-5″, C-8″), 132.4 (q, C-8″a, C-10′a), 134.1 (d, C-3″), 134.2, 134.3, 134.7 (3 * d, C-6″, C-7″, C-2‴), 136.9 (q, C-1″), 138.6 (q, C-2″), 148.1 (q, C-4″a), 171.4 (q, C-1), 181.3, 181.8 (2 * q, C-9″, C-10′), 197.4 (q, C-1″); MS (EI, 70 eV) 378 (2) [M^+], 350 (7), 322 (5), 306 (7), 266 (14), 251 (26), 190 (44), 164 (46), 99 (62), 85 (74), 53 (86). Anal. Calcd for $C_{22}H_{18}O_6$ C, 69.83; H 4.79. Found C, 69.39; H, 4.50.

4.7. 2-(4-Allyloxy-3-oxo-pentanoyl)-1-hydroxy-anthraquinone 12

Lithium hydride (110 mg, 13.8 mmol) was added at 0 °C under argon to a solution of ester **11** (295 mg, 0.78 mmol) in dry THF (78 mL) and the mixture was refluxed for 24 h. After cooling to 0 °C, dilute hydrochloric acid was added dropwise. The mixture was extracted with dichloromethane, the combined organic phases were washed with dilute hydrochloric acid, water, brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (dichloromethane) to afford dicarbonyl compound **12** (158 mg, 53% yield) as orange crystals, with a mp of 94–96 °C, and a small amount (83 mg, 40%) of anthraquinone **9**. $[\alpha]_D^{20} = -88$ (*c* 52, $CHCl_3$); UV (MeOH): λ_{max} ($\log\varepsilon$) = 203 nm (5.10), 232 (4.77), 252 (4.70); IR (KBr) 3447, 1637, 1592, 1560, 1475, 1424, 1358, 1326, 1304, 1283, 1207, 1107, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (d, $J_{5'-4'} = 6.9$ Hz, 3H, 5-H′), 4.02 (dddd, $J_{1''-1''} = 12.8$ Hz, $J_{1''-2''} = 6.0$ Hz, $J_{1''-3''cis} = J_{1''-3''trans} = 1.3$ Hz, 1H, 1-H″a), 4.4 (q, $J_{4'-5'} = 6.8$ Hz, 1H, 4-H′), 4.16 (dddd, $J_{1''-1''} = 12.8$ Hz, $J_{1''-2''} = 5.2$ Hz, $J_{1''-3''cis} = J_{1''-3''trans} = 1.4$ Hz, 1H, 1-H″b), 5.24 (dddd, $J_{3''-2''} = 10.4$ Hz, $J_{gem} = J_{3''-1''a} = J_{3''-1''b} = 1.3$ Hz, 1H, 3-H″*cis*), 5.35 (dddd, $J_{3''-2''} = 17.2$ Hz, $J_{gem} = J_{3''-1''a} = J_{3''-1''b} = 1.5$ Hz, 1H, 3-H″*trans*), 5.97 (dddd, $J_{2''-3''trans} = 17.2$ Hz, $J_{2''-3''cis} = 10.5$ Hz, $J_{2''-1''a} = 5.8$ Hz, $J_{2''-1''b} = 5.3$ Hz, 1H, 2-H″), 7.12 (sl, 1H, 2-H′), 7.81–7.85 (m, 3H, 4-H, 6-H, 7-H), 8.26, 8.30 (2 * m, 2 * 1H, 5-H, 8-H), 8.32 (d, $J_{3-4} = 8.8$ Hz, 1H, 3-H), 13.87 (s, 1H, OH-1), 15.74 (sl, 1H, OH-1″); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2 (q, C-5″), 70.9 (t, C-1″), 78.0 (d, C-4″), 98.8 (d, C-2″), 116.5 (s,

C-9a), 117.6 (t, C-3″), 118.7 (d, C-4), 127.1, 127.5 (2 * d, C-5, C-8), 128.6 (s, C-2), 133.0, 133.3, 134.5 (3 * s, C-4a, C-8a, C-10a), 134.2 (C-2″), 135.1, 135.2 (2 * d, C-6, C-7), 137.2 (s, C-1), 176.6 (s, C-1″), 181.8, 189.1 (2 * s, C-9, C-10), 202.0 (s, C-3″); MS (EI, 70 eV) 378 (20) [M^+], 350 (8), 322 (69), 294 (64), 266 (83), 167 (80), 139 (100), 85 (76), 77 (78), 41 (90); HRMS (EI, 70 eV, $C_{22}H_{18}O_6$): calcd 378.1103. Found 378.1107.

4.8. 2-(1-(Allyloxy)ethyl)-4*H*-naphtho[2,3-*h*]chromene-4,7,12-trione 13

A solution of diketoanthraquinone **12** (35 mg, 0.09 mmol) in trifluoroacetic acid (1.5 mL) was stirred 1 h at 0 °C, and 20 min at room temperature. After addition of dichloromethane, the solvent was removed under reduced pressure; dichloromethane was added and concentrated under reduced pressure three times to remove the trifluoroacetic acid. Purification by flash chromatography (dichloromethane/methanol 100/0 to 98/2) afforded anthrapyrane **13** (31 mg, 94% yield), with a mp of 152–153 °C (ethanol/toluene), as a pale yellow solid. $[\alpha]_D = -87$ (*c* 0.52, $CHCl_3$); UV (MeOH): λ_{max} (log ε) 207 nm (4.79), 232 (4.72), 253 (4.66), 352 (4.12); IR (KBr) 1681, 1655, 1590, 1417, 1310, 1283, 1270, 1119, 935 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, $J_{2'-1'} = 6.7$ Hz, 3H, 2-H′), 4.14 (dddd, $J_{1''-1''} = 12.8$ Hz, $J_{1''-2''} = 5.8$ Hz, $J_{1''-3''cis} = J_{1''-3''trans} = 1.3$ Hz, 1H, 1-H″a), 4.20 (dddd, $J_{1''-1''} = 12.8$ Hz, $J_{1''-2''} = 5.3$ Hz, $J_{1''-3''cis} = J_{1''-3''trans} = 1.4$ Hz, 1H, 1-H″b), 4.54 (q, $J_{1'-2'} = 6.7$ Hz, 1H, 1-H′), 5.24 (dddd, $J_{3''-2''} = 10.5$ Hz, $J_{gem} = J_{3''-1''a} = J_{3''-1''b} = 1.4$ Hz, 1H, 3-H″*cis*), 5.36 (dddd, $J_{3''-2''} = 17.1$ Hz, $J_{gem} = J_{3''-1''a} = J_{3''-1''b} = 1.5$ Hz, 1H, 3-H″*trans*), 5.96 (dddd, $J_{2''-3''trans} = 17.1$ Hz, $J_{2''-3''cis} = 10.5$ Hz, $J_{2''-1''a} = 5.8$ Hz, $J_{2''-1''b} = 5.3$ Hz, 1H, 2-H″), 6.61 (sl, 1H, 3-H), 7.80, 7.84 (2 * ddd, $J_{orthoa} = J_{orthob} = 7.4$ Hz, $J_{meta} = 1.7$ Hz, 2 * 1H, 9-H, 10-H), 8.27 (m, 1H, 8-H, 11-H), 8.32 (d, $J_{6-5} = 8.2$ Hz, 1H, 6-H), 8.59 (d, $J_{5-6} = 8.2$ Hz, 1H, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0 (q, C-2″), 70.9 (t, C-1″), 73.8 (d, C-1″), 108.6 (d, C-3), 117. (t, C-3″), 122.6 (s, C-12a), 123.1 (d, C-6), 127.1, 127.3 (2 * d, C-8, C-11), 128.3 (s, C-4a), 131.9 (d, C-5), 132.2 (s, C-7a or 11a), 133.9 (d, C-2″), 134.1, 134.8 (2 * d, C-9, C-10), 134.3 (s, C-7a or C-11a), 137.7 (s, C-6a), 154.6 (s, C-12a), 171.6 (s, C-2), 176.8 (s, C-4), 181.0 (s, C-12), 182.2 (s, C-7); MS (EI, 70 eV) 360 (11) [M^+], 318 (6), 304 (100), 266 (26), 252 (81), 222 (14), 189 (17), 167 (61), 139 (75), 85 (68), 41 (85); HRMS (EI, 70 eV, $C_{22}H_{16}O_5$): calcd 360.0998. Found 360.0992.

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