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Solid-Phase Synthesis of Decalin Scaffolds by Robinson Annulation with Immobilised Nazarov Reagents

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A method for the synthesis of natural product-inspired decalin systems on solid support is reported. It employs the Robinson annulation as key step and immobilised Nazarov reagents as key intermediates.

The development of compound collections by means of solid-phase synthesis is among the most frequently used technologies in chemical biology and medical chemistry research. In this context, natural product-guided compound library development has proven to be a viable strategy that delivers biologically prevalidated compound classes that often show relatively high hit rates at comparably small library size.[1,2] The development of efficient methods for the synthesis of natural product-inspired scaffolds and their subsequent structural variation in the format of solid-phase synthesis is therefore of considerable interest.

The decalin scaffold is among the most frequently occurring compound frameworks found in nature,[3] and natural products incorporating diversely substituted decalins display multiple biological activities (Figure 1).[4]

Given this biological relevance of the decalin scaffold we have explored possibilities for the synthesis of decalins on solid supports.[5] The Robinson annulation is among the most powerful methods for assembling decalins,[6] but no Robinson annulations on resin have yet been described.

Here we report on the development of a solid-phase Robinson annulation decalin synthesis employing polymer-bound Nazarov reagents as building blocks.

The Nazarov reagent **1** is a methyl vinyl ketone derivative that has been broadly used in natural product synthesis.[7] If employed in the construction of decalins it introduces an ester that offers potential for further subsequent functionalisation. It was therefore planned to develop analogues of the Nazarov reagent that would incorporate an additional alcohol (e.g., **2**) as a functional group for linkage to the polymeric carrier (Scheme 1). It was planned to investigate whether the Wang linker itself or alternatively a silyl linker based on the Wang linker would be more suitable for immobilisation of the reagent (see **3** and **4**, Scheme 1).

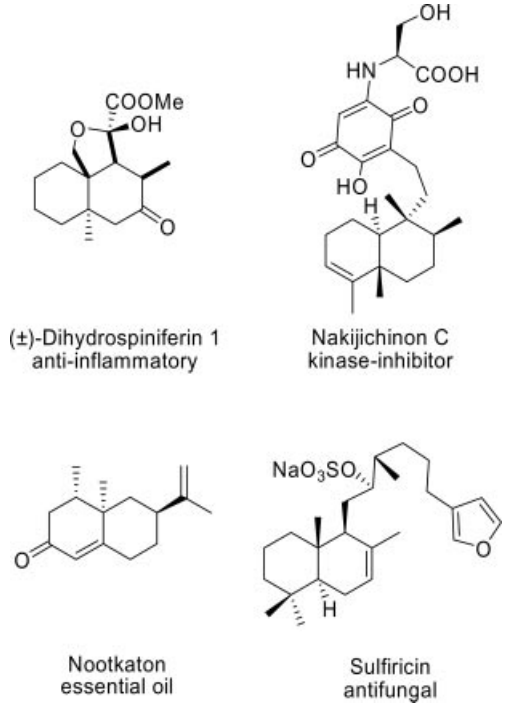

Figure 1. Examples of natural products with decalin structure and their biological activity.

For the synthesis of the immobilised reagents, butynediol **5** (Scheme 2) was converted into the monoprotected diols **6** and **7** by established methods.[8] Intermediate **6** carried a fluoride-labile TBS blocking function, whereas for **7** an acid-labile trimethoxytrityl (TMT) group was employed. The silyl-protected alcohol was coupled to the resin after activation of the Wang linker as a trichloroacetimidate.[9] The TBS group was then removed and the loading was de-

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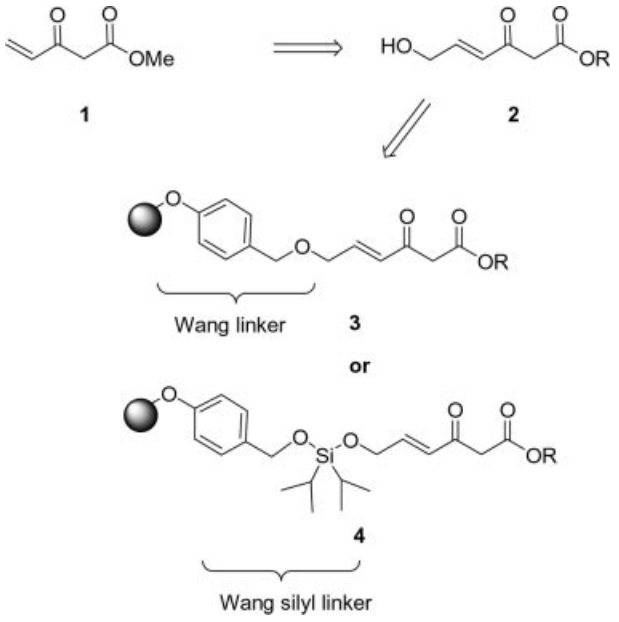
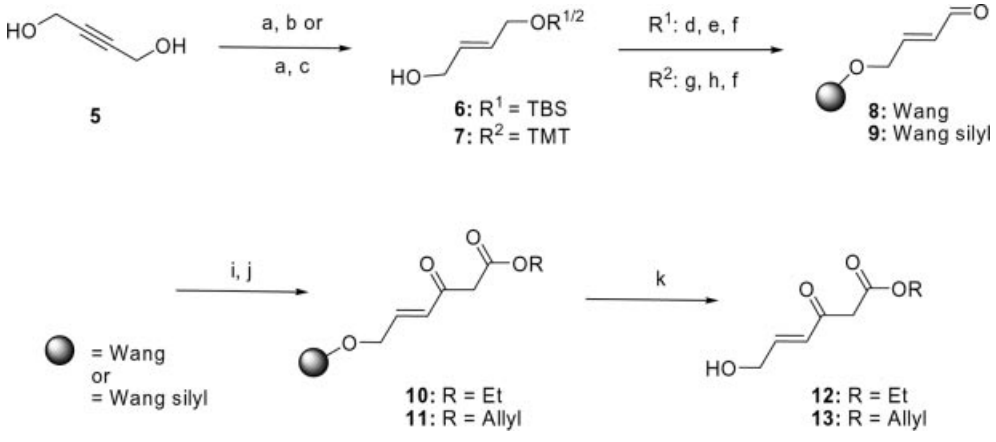


Scheme 1. Structure of the Nazarov reagent **1** and design of a polymer-bound analogue.

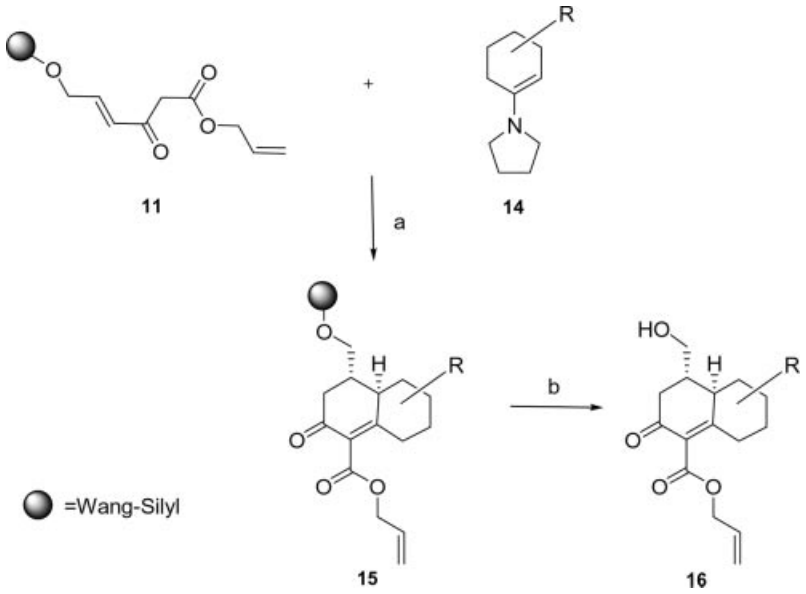
termined to be 1.06 mmol g^{-1} by the Fmoc method.[10] Subsequent oxidation to the aldehyde **8** proceeded best if IBX was employed as oxidant – use of, for example, SO_3·pyridine or the Dess–Martin periodinane gave inferior results. The aldehyde was formed in 95% yield (DNPH method).[5] For the synthesis of aldehyde **9** the Wang linker was first treated with $(iPr)_2SiCl_2$, followed by the TMT-protected alcohol **7**, and the selective removal of the TMT group was accomplished by treating the polymer twice with 0.5 M formic acid for one minute. The deprotection could be readily followed by UV determination of the formed trityl cation at 484 nm[11] and the loading was determined to be 0.64 mmol g^{-1} (53% for three steps). In this case oxidation to the aldehyde proceeded best if the Dess–Martin periodinane was employed. Determination of the loading by the FmPH method[12] revealed that the yield for this step was 95%.

Both resins then were subjected to aldol reactions with the lithium enolates of acetic acid ethyl or allyl ester (Scheme 2). To obtain preparatively viable yields it was important to pre-swell the resin in THF and to activate the aldehyde by pre-treatment with BF_3·Et_2O. The resulting β-hydroxyesters were then oxidised again with IBX (Wang linker) or Dess–Martin periodinane (Wang silyl linker) to yield immobilised β-keto esters **10** and **11**. Analogues of Nazarov reagents **12** and **13** could be released from the solid supports by treatment with TFA in CH_2Cl_2 (3%) or TBAF in CH_2Cl_2 (1 M), respectively and were obtained in 18% (**12**) and 16% (**13**) yields over six steps on the polymeric carrier.[13]

For the subsequent Robinson annulation, resin-bound β-keto ester **11** (Scheme 3) with the silyl linker was chosen and the reaction conditions were optimised in solution with the analogous TBS-protected compound. This exercise found that a 1:3 mixture of dioxane and methanol, together with NaOMe or DBU as base, gave the best results if resin **11** was treated with enamines at 50 °C. These conditions were then employed for the Robinson annulations on the solid phase. As demonstrated in Scheme 3, polymer-linked β-keto ester **11** reacted with differently substituted enamines **14** (Table 1) under these conditions to yield polymer-bound decalins **15**. Investigation of the resin obtained from enamine **14a** by MAS-NMR confirmed product formation. The desired condensation products were released from the polymeric carrier in yields of 28–37% by treatment with TBAF in THF.[13] GC and NMR spectroscopic examinations showed that only one stereoisomer was formed



Scheme 2. Synthesis of immobilised analogues of the Nazarov reagent: a) $LiAlH_4$, THF, reflux, 72%. b) NaH, THF, TBSCl, 0 °C to room temp., 82%. c) NaH, TMTCl, toluene/DMF, 1:1, 21%. d) Resin with Wang linker, Cl_3CCN, CH_2Cl_2, DBU, 0 °C, alcohol **6**, CH_2Cl_2, BF_3·Et_2O, room temp. e) 1 M TBAF in THF, room temp. 89% (two steps, Fmoc method). f) IBX, THF/DMSO, 1:1, room temp., 95% or Dess–Martin periodinane, CH_2Cl_2, room temp., 95% (DNPH/FmPH methods). g) Resin with Wang linker, CH_2Cl_2, $(iPr)_2SiCl_2$, lutidine, DMAP, alcohol, room temp. h) 0.5 M HCOOH in CH_2Cl_2, 2×1 min, room temp., 53% (3 steps). i) $(iPr)_2NH$, *n*BuLi, CH_3COOEt or $CH_3COOAllyl$, THF, BF_3·Et_2O, –60 °C to rt. j) IBX, THF/DMSO, 1:1, room temp., or Dess–Martin periodinane, CH_2Cl_2, room temp. k) 3%TFA/1 M TBAF in CH_2Cl_2, room temp. (overall yield Et: 18%, Allyl: 16%).



Scheme 3. Robinson annulation on solid phase with an immobilised Nazarov reagent: a) MeOH/dioxane 3:1, 50 °C, then base. b) TBAF, THF, room temp., overnight, yields see Table 1.

(*de* >98%), containing the proton at the angular carbon and next to the –CH_2–OH substituent at an angle of 100–120°[14] (Table 1).

These examples demonstrate that the method described here gives access to differently substituted decalins in a preparatively viable manner. It should be amenable to further variation and extension (e.g., the acetal protecting group and an appropriate N-protecting group incorporated into enamines similar to those shown in Scheme 1 might be cleaved on the polymeric carrier, opening up opportunities for further derivatisations). Furthermore, selective cleavage of the ester and/or further functionalisations through additional substituents in an aromatic ring incorporated into the enamine part (see Scheme 3) could be envisaged.

Experimental Section

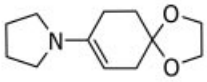
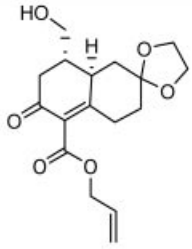
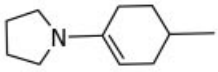
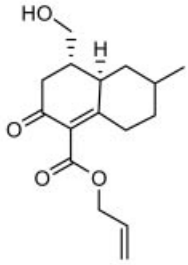
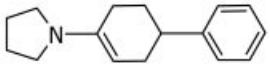
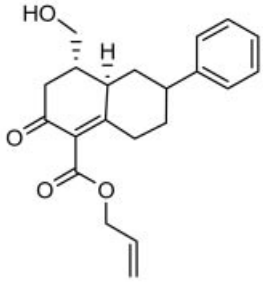
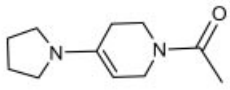
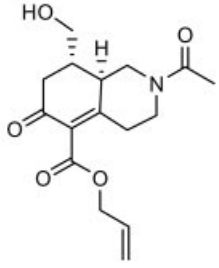
General Procedures: All reactions were carried out under argon. All solvents were distilled by standard procedures before use. CH_2Cl_2 was distilled under argon from CaH_2, MeOH was distilled under argon from Mg. All other chemicals were purchased from commercial sources and were used without further purification. Yields refer to isolated and pure compounds unless otherwise stated. ^{1}H and ^{13}C NMR spectroscopic data were recorded on a Varian Mercury 400 spectrometer. FAB and EI measurements were taken with a Jeol SX instrument with use of a 3-nitrobenzyl alcohol (3-NBA) matrix. GC-MS analysis was performed on a Hewlett–Packard HP 5890-series II gas chromatograph with a HP 5972-series mass selective detector. Chiral GC measurements were performed with an Agilent 6890N and a Lipodex-E column. HPLC purifications were performed with an Agilent 1100 Series fitted with either a Nucleosil 102–7 C4 or a Nucleodur C18 column (Macherey–Nagel) and with acetonitrile and Millipore water containing 0.1% of TFA. Usual methods start with 5% acetonitrile and go up to 100% within 20 minutes. Flash chromatography was performed with silica gel (60, 40–63 μm) from Acros. TLC was performed with aluminium-backed silica 60 F254 plates (Merck) with UV as visualising agent and an ethanolic solution of phosphomolybdic acid and heat as developing agents.

***trans*-Butene-1,4-diol:** A solution of lithium aluminium hydride (5.3 g) in dry THF (200 mL) was cooled to –78 °C. A solution of butyne-1,4-diol (10 g, 0.11 mol) in dry THF (20 mL) was added under argon with vigorous stirring. After completion of addition the mixture was heated at reflux for 18 h, cooled (ice bath) and quenched carefully with saturated NH_4Cl solution. The resulting precipitate was filtered through celite and the filter cake was washed thoroughly with diethyl ether. The organic layer was concentrated to dryness and the crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 1:10 to pure ethyl acetate) to give the diol (7.02 g, 0.08 mol, 72%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88 (m, 2 H), 4.17 (m, 4 H), 1.89 (2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 130.5, 62.9 ppm. IR (KBr): $\tilde{\nu}$ = 3350 (s, alcohol) cm^{-1}. GC-MS (*m*/*z*, rel. int.%): 88 [*M*]$^+$ (5), 70 (8), 61 (12), 57 (7), 43 (100).

***trans*-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol (6):** NaH (60 wt.-% in oil, 200 mg, 5 mmol) was added at 0 °C to a solution of *trans*-butene-1,4-diol (441 mg, 5 mmol) in dry THF 20 mL and the mixture was stirred for 1 h at room temperature. A solution of TBS-Cl (0.755 g) dissolved in dry THF was added dropwise and the mixture was stirred for 2 h at room temperature, quenched with saturated NH_4Cl solution and extracted with diethyl ether (3 × 60 mL). The combined organic layers were washed with saturated sodium chloride solution, dried ($MgSO_4$) and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 10:1) to give the alcohol **6** (829 mg, 4.1 mmol, 82%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (dt, *J* = 5, 11 Hz, 1 H), 5.79 (dt, *J* = 4, 8 Hz, 1 H), 4.18 (d, *J* = 4, 2 H), 4.16 (d, *J* = 5 Hz, 2 H), 1.48 (1 H), 0.91 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.0, 128.9, 63.2, 63.1, 25.9, 14.4, –5.3 ppm. IR (KBr): $\tilde{\nu}$ = 3338 (s, alcohol) cm^{-1}. GC-MS (*m*/*z*, rel. int.%): for $C_{10}H_{28}O_4Si$, *M* = 202.4 g mol^{-1}, 184 [*M* – H_2O]$^+$ (23), 171 (12), 145 [*M* – *tert*-butyl]$^+$ (53), 75 (100).

***trans*-4-[(Trimethoxytrityl)oxy]but-2-en-1-ol (7):** NaH (60 wt.-% in oil, 200 mg, 5 mmol) was added at 0 °C to a solution of *trans*-but-

Table 1. Decalins synthesized on solid support.

Entry	Enamine	Base	Decalin		Yield [%]
1	 **4a**	DBU		**16a**	31%
2	 **4b**	NaOMe		**16b**	32%
3	 **4c**	NaOMe		**16c**	28%
4	 **4d**	DBU		**16d**	37%

ene-1,4-diol (441 mg, 5 mmol) in dry toluene (20 mL) and the mixture was stirred for 1 h at room temperature. A solution of TMTCl (1.84 g) in dry toluene/DMF was added dropwise and the mixture was stirred for a further 1 h at room temperature. The mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ solution, water and saturated sodium chloride solution and dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate, 4:1) to give the alcohol **7** (440 mg, 1.05 mmol, 21%) as an orange oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 9 Hz, 2 H), 7.24 (d, J = 9 Hz, 2 H), 7.17 (d, J = 9 Hz, 2 H), 6.83 (d, J = 9 Hz, 4 H), 6.75 (d, J = 9 Hz), 5.79–5.70 (m, 2 H), 4.22 (d, J = 2 Hz, 2 H), 4.04 (d, J = 6 Hz, 2 H), 3.80–3.74 (m, 9 H), 2.18 (1 H) ppm. IR (KBr): $\tilde{\nu}$ = 3415 (s, alcohol), 825 (m, subst. benzene) cm^{-1}. HRMS [FAB/HR] for $C_{26}H_{28}O_5$, M = 420.5 g mol^{-1}, calculated: $[M + H]^+$: 420.1937; found 420.1908.

Wang-Supported *trans*-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol. Loading of the Resin (Polystyrene, Wang Linker): Trichloroacetonitrile (1.84 mL) was added to a suspension of resin (1 g, 1.2 mmol g^{-1}) swollen in dry dichloromethane (10–12 mL) and the suspension was cooled to 0 °C. Afterwards, DBU (0.15 mL) was added dropwise over a period of 5 minutes. The orange solution was shaken for 40 minutes at 0 °C, and the resin was filtered and washed five times with dichloromethane and dried under reduced pressure. IR: $\tilde{\nu}$ = 1664 (nitrile) cm^{-1}. The resin was again swollen in dry dichloromethane (8 mL) and *trans*-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol (**6**, 2.02 g, 4.8 mmol, 4 equiv.) was added. After the mixture had been kept for 5 minutes at room temperature, $BF_3{\cdot}Et_2O$ (52.5 μL) was added and the suspension was shaken at room temperature overnight. The resin was filtered, washed five times with dichloromethane and once with methanol and dried under reduced pressure. Yield: 1.22 g colourless beads; the loading was determined after deprotection.

Wang-Supported *trans*-4-[(Trimethoxytrityl)oxy]but-2-en-1-ol. Loading of Resin with a Wang-Diisopropylsilyl Linker: Well dried Wang linker (500 mg, 1.2 mmol g^{-1}) was swollen in dry dichloro-

methane (5 mL) under argon. After addition of lutidine (580 μL, 10 equiv.), DMAP (61 mg, 1 equiv.) and dichlorodiisopropylsilane (271 μL, 3 equiv.) the suspension was shaken for 3 h at room temperature. The resin was washed three times with dry dichloromethane under argon and dried under reduced pressure. After swelling in dry dichloromethane, lutidine (580 μL, 10 equiv.), DMAP (61 mg, 1 equiv.) and *trans*-[4-(trimethoxytrityl)oxy]but-2-en-1-ol (**7**, 440 mg 2 equiv.) were added and the suspension was shaken at room temperature overnight. The resin was filtered, washed five times with dichloromethane and dried under reduced pressure. Yield: 645 mg yellow beads; the loading was determined after deprotection.

Wang-Supported *trans*-But-2-ene-1,4-diol: For deprotection of the TBS-protected alcohol the resin (610 mg) was swollen for 10 minutes in THF and filtered. TBAF solution (1 M in THF, 3 mL, 3 equiv.) was added and the suspension was shaken at room temperature overnight. The resin was filtered, washed twice each with THF, dichloromethane and methanol and dried under reduced pressure. Yield: 550 mg yellow beads, 1.07 mmol g^{-1} (90%, two steps); the loading was detected by the Fmoc method. IR: $\tilde{\nu}$ = 3415 (s, alcohol) cm^{-1}.

Wang-Supported *trans*-But-2-ene-1,4-diol: For deprotection of the TMT-protected alcohol the resin (200 mg) was swollen for 10 minutes in dichloromethane and filtered. A solution of HCOOH in CH_2Cl_2 solution (0.5 M, 2 mL) was added to the resin (2× 1 minute), followed by washing six times with dichloromethane and once with ethyl acetate and drying under reduced pressure. Yield: 191 mg colourless beads, 0.64 mmol g^{-1} (53%, two steps); the loading was determined by the quantitative UV detection of the released trityl cation. IR: $\tilde{\nu}$ = 3440 (s, alcohol) cm^{-1}.

Wang-Supported *trans*-1-Oxobut-2-en-4-ol (8): The resin (500 mg, 1.07 mmol g^{-1}) was swollen for 10 minutes in THF and filtered. A solution of IBX (5 equiv.) in DMSO/THF (4 mL, 1:1) was added and the suspension was shaken at room temperature overnight. The resin was washed three times each with DMSO, DMSO/THF (1:1), THF and CH_2Cl_2 and once with MeOH and dried under reduced pressure. Yield: 490 mg colourless beads, 1.01 mmol g^{-1} (95%); the loading was determined by the DNPH method and the yield was calculated from the loading. IR: $\tilde{\nu}$ = 1695 (s, aldehyde) cm^{-1}.

Wang-Supported *trans*-1-Oxobut-2-en-4-ol (9): The resin (191 mg, 0.64 mmol g^{-1}) was swollen for 10 minutes in dichloromethane and filtered. A solution of Dess–Martin periodinane (15 wt.-% in DCM, 5 equiv.) was added and the suspension was shaken 5 h at room temperature. The resin was washed five times with CH_2Cl_2 and once with MeOH and dried under reduced pressure. Yield: 185 mg colourless beads, 0.61 mmol g^{-1} (95%); the loading was detected by the FmPH method and the yield was calculated from the loading. IR: $\tilde{\nu}$ = 1700 (s, aldehyde) cm^{-1}.

Wang-Supported Ethyl 6-Hydroxy-3-oxohex-4-enoate (10): The anion (20 equiv.) was prepared under argon at –78 °C. To this end a solution of *n*-butyllithium in hexane (2.5 M, 5.45 mmol, 1.74 mL) was added dropwise at –78 °C to a solution of diisopropylamine (0.61 mL, 5.45 mmol) in dry THF (20 mL) and the mixture was stirred for 25 minutes. A solution of ethyl acetate (0.32 mL, 4 mmol) in THF was added dropwise and the mixture was stirred for 50 minutes at –78 °C. Resin (200 mg, 1.0 mmol g^{-1}) was swollen in a small amount of dry THF and cooled to –60 °C, after which $BF_3{\cdot}Et_2O$ (0.1 mL) was added and the suspension was shaken for 5 minutes. The solution of the anion was added and the suspension was shaken for 6 h at –60 °C and then allowed to warm up slowly to room temperature overnight. The reaction was quenched with THF/water and the resin was filtered. It was washed three times each with THF and CH_2Cl_2 and once with MeOH and dried under reduced pressure. Yield: 240 mg yellow beads. IR: $\tilde{\nu}$ = 3496 (s, alcohol) cm^{-1}. The product was used without further analysis. The resin (495 mg, 0.8 mmol g^{-1}) was swollen for 10 minutes in THF and filtered. A solution of IBX (2.4 mmol, 671 mg, 6 equiv.) in DMSO/THF (1:1, approximately 5 mL) was added and the suspension was shaken at room temperature overnight. The resin was washed three times each with DMSO, DMSO/THF (1:1), THF and CH_2Cl_2 and once with MeOH and dried under reduced pressure. Yield: 480 mg yellow beads. IR: $\tilde{\nu}$ = 1735 (s, ester) cm^{-1}. The product was detected by cleavage (see below).

Wang-Supported Allyl 6-Hydroxy-3-oxohex-4-enoate (11): The anion (20 equiv.) was prepared under argon at –78 °C. To this end a solution of *n*-butyllithium in hexane (2.5 M, 5.45 mmol, 1.74 mL) was added dropwise at –78 °C to a solution of diisopropylamine (0.61 mL, 5.45 mmol) in dry THF (20 mL) and the mixture was stirred for 25 minutes. A solution of allyl acetate (0.34 mL, 4 mmol) in THF was added dropwise and the mixture was stirred for 50 minutes at –78 °C. Resin (330 mg ≈ 0.6 mmol g^{-1}) was swollen in a small amount of dry THF and the mixture was cooled to –60 °C, after which $BF_3{\cdot}Et_2O$ (0.1 mL) was added and the suspension was shaken for 5 minutes. The solution of the anion was added and the suspension was shaken for 6 h at –60 °C and then allowed to warm up slowly to room temperature overnight. The reaction was quenched with THF/water and the resin was filtered. It was washed three times each with THF and CH_2Cl_2 and once with MeOH and dried under reduced pressure. The product was immediately used without further analysis.

The resin was swollen for 10 minutes in dichloromethane and filtered. A solution of 5 equiv. Dess–Martin periodinane (15 wt.-% in CH_2Cl_2, 5 equiv.) was added and the suspension was shaken overnight at room temperature. The resin was washed five times with CH_2Cl_2 and once with MeOH and dried under reduced pressure. Yield: 360 mg colourless beads. The product was detected by cleavage (see below).

Ethyl 6-Hydroxy-3-oxohex-4-enoate (12): After swelling in dichloromethane, resin (200 mg) was treated with TFA in CH_2Cl_2 (3%, 1 mL, 3 × 20 min). The combined solutions were neutralised with solid Na_2CO_3, filtered and concentrated. The crude product was purified by flash chromatography (silica gel, toluene/methanol, 8:1) to give the alcohol **12** (6.1 mg, 18% overall yield) as a colourless oil. R_f (toluene/methanol, 5:1 v/v) = 0.22. Keto/enol ratio 1.8:1. ^1H NMR (500 MHz, $CDCl_3$): δ = 11.86 (s, 0.36 H), 6.96 (dt, J = 4, 16 Hz, 0.64 H), 6.76–6.71 (m, 0.36 H), 6.46 (d, J = 16 Hz, 0.64 H), 6.22 (s, 0.36 H), 6.07 (d, J = 16 Hz, 0.36 H), 4.38 (m, 2 H), 4.34 (q, J = 2 Hz, 2 H), 3.67 (s, 1.28 H), 2.04 (s, 1 H), 1.27 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.9, 170.0, 169.2, 165.9, 142.0, 138.1, 127.1, 123.1, 91.4, 61.2, 60.2, 62.2, 61.5, 47.4, 14.1, 14.0 ppm. IR: $\tilde{\nu}$ = 3420 (s, alcohol) cm^{-1}. HRMS [FAB/HR] for $C_8H_{12}O_4$, M = 172.18 g mol^{-1}, calculated: $[M + H]^+$: 173.0816; found 173.0799.

Allyl 6-Hydroxy-3-oxohex-4-enoate (13): After swelling in dichloromethane, resin (200 mg) was treated overnight with TBAF in CH_2Cl_2 (1 M, 1 mL). After additional washing of the resin with dichloromethane the combined solutions were washed with saturated $NaHCO_3$ solution, water and saturated sodium chloride solution and dried ($MgSO_4$). The crude product was purified by flash chromatography (silica gel, toluene/methanol, 9:1) to give the alcohol **13** (4.6 mg, 16% overall yield) as a colourless oil. R_f (toluene/methanol, 5:1 v/v) = 0.26. Keto/enol ratio 3:2. ^1H NMR (500 MHz, $CDCl_3$): δ = 11.77 (s, 0.4 H), 6.96 (dt, J = 4, 16 Hz, 0.6 H), 6.75 (dt, J = 4, 16 Hz, 0.6 H), 6.46 (dt, J = 2, 16 Hz, 0.4 H),

6.08 (dd, J = 2, 16 Hz, 0.4 H), 5.93 (m, 1 H), 5.34 and 5.26 (m, each 1 H), 5.05 (s, 0.4 H), 4.66 (dt, J = 1, 6 Hz, 0.8 H), 4.64 (dt, J = 1, 6 Hz, 1.2 H), 3.64 (s, 1.2 H), 4.40 (s, 1.2 H), 4.35(s, 0.8 H), 2.45 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.0, 172.4, 168.9, 167.2, 147.8, 138.4, 131.3, 131.9, 131.8, 118.8, 118.4, 90.9, 70.6, 67.4, 65.6, 47.0 ppm. IR: $\tilde{\nu}$ = 3426 (s, alcohol) cm^{-1}. HRMS [FAB/LR] for $C_9H_{12}O_4$, M = 184.19 g mol^{-1}, calculated: $[M + H]^+$: 185.08; found 185.03.

Allyl 6,6-(Ethylenedioxy)-2,3,4,4a,5,6,7,8-octahydro-4-(hydroxymethyl)-2-oxonaphthalene-1-carboxylate (16a): A mixture of cyclohexane-1,4-dione monoethylene acetal (0.11 g, 0.7 mmol), pyrrolidine (0.29 mL, 3.5 mmol) and toluene (5 mL) was heated at reflux in a toluene-filled Dean–Stark water separator until the conversion into the enamine was complete (monitored by GC-MS). The solvent and excess pyrrolidine were removed under reduced pressure, yielding the pure enamine as a pale yellow oil, which was stored under argon and dissolved in dry (!) methanol/1,4-dioxane (3:1, 0.7 mL). A suspension of polymer-bound alcohol (100 mg, 0.7 mmol g^{-1}) in methanol/1,4-dioxane was swollen, after which the dissolved enamine was added. The suspension was shaken at 50 °C for 20 h, and, after addition of base (3 equiv.), for an additional 24 h. Afterwards the solution was quenched with water/THF and the resin was filtered off. It was washed three times each with THF and CH_2Cl_2, twice with HCOOH in CH_2Cl_2 (0.5 M, 5 s), five times with CH_2Cl_2 and once with MeOH and dried under reduced pressure. IR: $\tilde{\nu}$ = 1739 (s, ester) cm^{-1}. The crude product was cleaved from the solid support by treatment of the resin with TBAF in THF (1 M) at room temperature overnight. The resin was washed twice with THF and the combined organic phases were washed with saturated $NaHCO_3$ solution and saturated sodium chloride solution and dried ($MgSO_4$). Purification was achieved by preparative HPLC. Yield: 7 mg (0.022 mmol, 31%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08–5.84 (m, 1 H), 5.32 (m, 2 H), 4.74 (d, J = 15 Hz), 3.99 (s, 4 H), 3.79–3.58 (m, 2 H), 2.82–2.68 (m, 1 H), 2.60–2.45 (m, 2 H), 2.19–2.14 (d, J = 11 Hz, 1 H), 2.00–1.72 (m, 3 H), 1.62–1.42 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.4, 166.0, 164.4, 131.6, 118.6, 107.6, 66.5, 64.6, 64.6, 67.1, 38.8, 37.1, 31.3, 29.7, 24.3, 19.9 ppm. HRMS [FAB/HR] for $C_{17}H_{22}O_6$, M = 322.35 g mol^{-1}, calculated: $[M + H]^+$: 323.1496; found 323.1510.

16b: Resin (100 mg) was treated with *p*-methylcyclohexanone (10 equiv.) as described for compound **16a**. IR: $\tilde{\nu}$ = 1716 (s, ester) cm^{-1}. The crude product was cleaved from solid support by treatment of the resin with TBAF in THF (1 M) at room temperature overnight. The resin was again washed twice with THF and the combined organic phases were washed with saturated $NaHCO_3$ solution and saturated sodium chloride solution and dried ($MgSO_4$). Purification was achieved by preparative HPLC. Yield: 6.2 mg (0.0224 mmol, 32%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08–5.82 (m, 1 H), 5.34–5.28 (m, 2 H), 4.74 (d, J = 15 Hz), 3.78–3.56 (m, 2 H), 2.82–2.68 (m, 1 H), 2.60–2.45 (m, 2 H), 2.19–2.14 (d, J = 12 Hz, 1 H), 1.98–1.76 (m, 4 H), 1.58–1.44 (m, 3 H), 0.82 (s, 3 H) ppm. HRMS [FAB/HR] for $C_{16}H_{22}O_4$, M = 278.34 g mol^{-1}, calculated: $[M + H]^+$: 279.1598; found 279.1613.

16c: Resin (100 mg) was treated with *p*-phenylcyclohexanone (10 equiv.) as described for compound **16a**. IR: $\tilde{\nu}$ = 1739 (s, ester) cm^{-1}.

The crude product was cleaved from solid support by treatment of the resin with TBAF in THF (1 M) at room temperature overnight. The resin was again washed twice with THF and the combined organic phases were washed with saturated $NaHCO_3$ solution and saturated sodium chloride solution and dried ($MgSO_4$). Purification was achieved by preparative HPLC. Yield: 6.7 mg (0.02 mmol, 28%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 5 Hz, 2 H), 7.24–7.19 (m, 3 H), 5.99–5.82 (m, 1 H), 5.36–5.30 (m, 2 H), 4.72 (d, J = 15 Hz), 3.78–3.56 (m, 2 H), 2.80–2.68 (m, 1 H), 2.60–2.45 (m, 2 H), 2.19–2.14 (d, J = 12 Hz, 1 H), 1.98–1.76 (m, 4 H), 1.58–1.44 (m, 3 H) ppm. HRMS [FAB/HR] for $C_{15}H_{20}O_4$, M = 340.41 g mol^{-1}, calculated: $[M + H]^+$: 341.1755; found 341.1802.

Allyl *rac*-2-Acetyl-1,2,3,4,6,7,8,8a-octahydro-4-(hydroxymethyl)-6-oxoisoquinolin-5-carboxylate (16d): Resin (100 mg) was treated with *N*-acetylpiperidone (10 equiv.) as described for compound **16a**. IR: $\tilde{\nu}$ = 1739 (s, ester) cm^{-1}.

The crude product was cleaved from solid support by treatment of the resin with TBAF in THF (1 M) at room temperature overnight. The resin was again washed twice with THF and the combined organic phases were washed with saturated $NaHCO_3$ solution and saturated sodium chloride solution and dried ($MgSO_4$). Purification was achieved by preparative HPLC. Yield: 8 mg (0.026 mmol, 37%), colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08–5.84 (m, 1 H), 5.32 (m, 2 H), 4.74 (d, J = 15 Hz), 3.86 (dq, J = 2, 9 Hz, 1 H), 3.79–3.58 (m, 2 H), 3.21–3.13 (m, 1 H), 2.82–2.59 (m, 2 H), 2.60–2.45 (m, 2 H), 2.10–1.96 (m, 1 H), 2.00–1.72 (m, 3 H) ppm. HRMS [FAB/HR] for $C_{16}H_{21}NO_5$, M = 307.34 g mol^{-1}, calculated: $[M + H]^+$: 308.1500; found 308.1524.

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[13] Examination of the solvents used in the reactions and for washing of the resin by GC-MS showed that premature cleavage of intermediates from the resin did not occur under the described conditions.
[14] For assignment of relative configurations the NMR spectra of the products were compared with those of analogous compounds masked as *tert*-butyldimethylsilyl ethers and synthesized by solution-phase reactions by established methods.

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