publication no. CCDC-142907 (**1A**) and CCDC-142908 (**1B**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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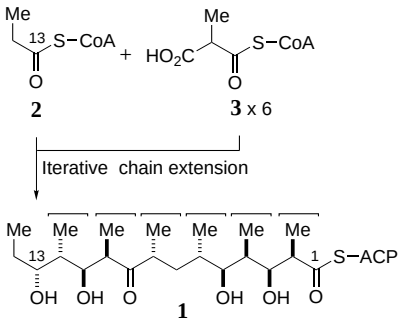
A Combinatorial Approach to Polyketide-Type Libraries by Iterative Asymmetric Aldol Reactions Performed on Solid Support**

Ian Paterson,* Monica Donghi, and Kai Gerlach

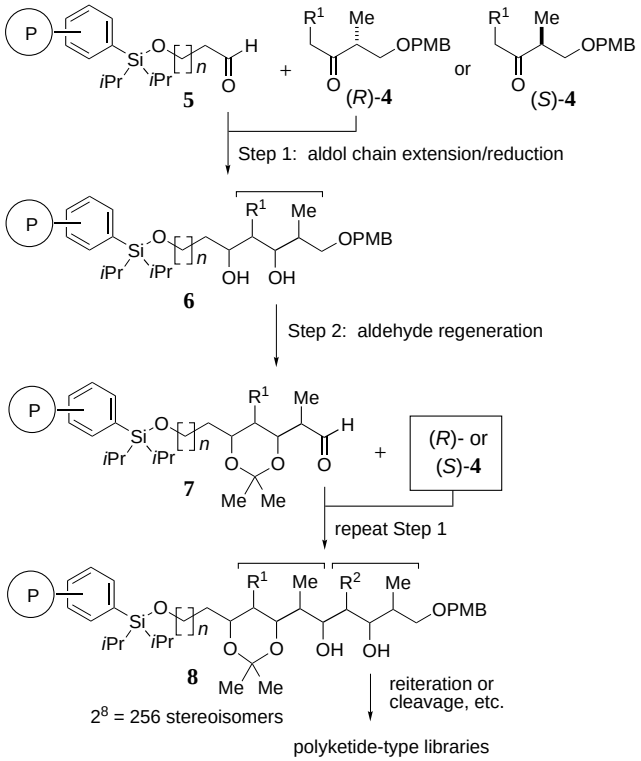
The polyketides represent a rich reservoir of structurally complex, bioactive, natural products, with many having therapeutic importance (as antibiotics, anticancer agents, antifungals, antiparasitics, immunosuppressants, and cardiovascular agents).[1] As a source of pharmaceutically relevant, molecular diversity, they are attractive targets for developing a combinatorial approach to library generation, particularly if this can be accomplished on solid phase, where purification procedures are simplified and automation becomes feasible. Solid-phase synthesis, routinely applied to the preparation of peptides and oligonucleotides, has been adapted in recent years to oligosaccharides and small molecules.[2] However, the synthesis of elaborate polyketide sequences (e.g. **1**, the acyclic precursor of the erythromycin antibiotics, Scheme 1) involving the controlled formation of multiple stereocenters remains a challenge,[3, 4] requiring the transfer of more sophisticated chemistry for achieving asymmetric carbon–carbon formation to solid phase.

In the archetypal case of erythromycin, the heptaketide precursor **1** is assembled biosynthetically by the polyketide synthase from a starter unit **2** and six extender units **3**, with the growing chain bound to the acyl carrier protein (ACP).[5, 6] By mimicking this processive mechanism in the laboratory using a greater variety of chain extending units, a combinatorial synthetic approach might be developed, leading to much greater molecular diversity. As part of studies towards this goal,[3] herein we demonstrate the utility of the chiral ketones **4** (see Scheme 2) for performing efficient polyketide synthesis on solid support, providing wide-ranging opportunities for structural and stereochemical diversification.



Scheme 1. Biosynthesis of the heptaketide precursor **1** of erythromycin. ACP = acyl carrier protein. CoA = coenzyme A.

In this new approach to expanding polyketide diversity (Scheme 2), a suitable aldehyde starter unit, such as **5**, is attached to a polystyrene support (which functions as a surrogate for the ACP) through a silyl ether linker. By using stereoregulated aldol chemistry, employing the reagents (*R*)- or (*S*)-**4** for chain extension and a subsequent ketone reduction to produce the 1,3-diol **6** (Step 1), followed by regeneration of the aldehyde functionality in **7** (Step 2), repetition provides the more elaborate 1,3-diol **8**. This leads progressively to the synthesis of polyketide-type sequences of



Scheme 2. Solid-phase synthesis of polyketide-type libraries using iterative chain extension of resin-supported aldehydes **5** and **7** with ketones (*R*)- or (*S*)-**4**. P = polystyrene resin (styrene–1% divinylbenzene, 200–400 mesh), PMB = *p*-methoxybenzyl.

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increasing complexity, where the spacer ($HOCH_2CH_2CH_2$ for $n=2$) is incorporated into the final product. After a single iteration, the resulting sequence **6** has four contiguous stereocenters (16 possible stereoisomers), while a second iteration to give **8** introduces eight contiguous stereocenters (corresponding to 256 possible stereoisomers for $R^1=R^2=Me$). By varying the substitution on the reagent module **4** in a combinatorial sense, many additional opportunities for structural diversification in **6** and **8** are possible, leading potentially to even larger libraries.

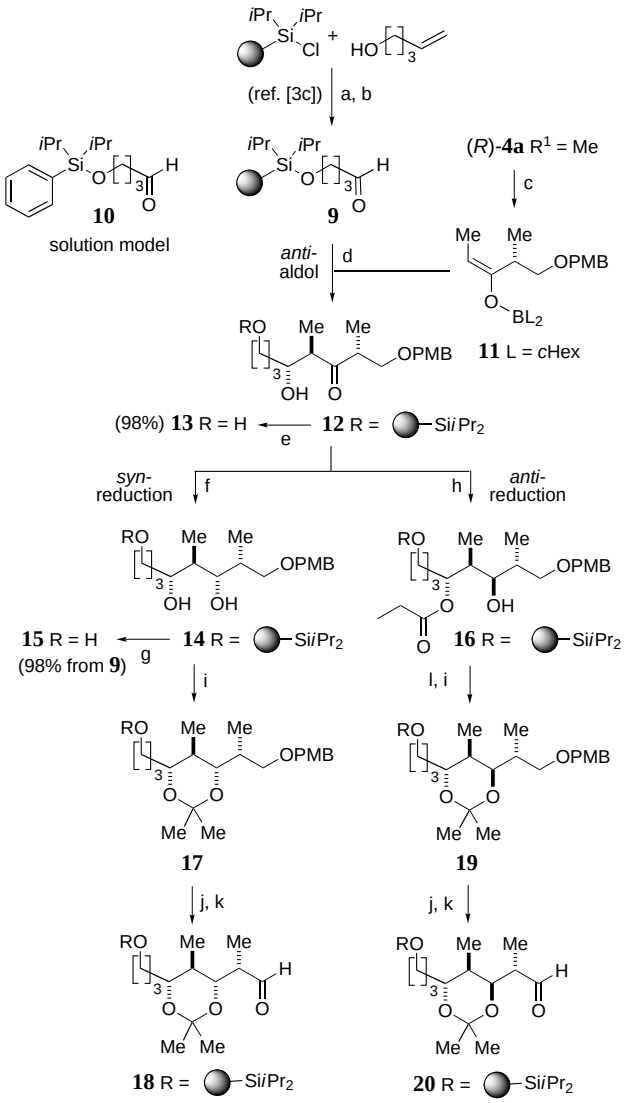
As shown in Scheme 3, the viability of performing stereocontrolled aldol reactions and reductions in an iterative fashion on a suitable solid-supported aldehyde was first examined. The resin-bound aldehyde **9** was prepared[7] by attachment of 4-penten-1-ol to chlorodiisopropylsilyl polystyrene, followed by ozonolysis with a reductive workup (Ph_3P, sonication); its loading was determined as 0.75 mmol g^{-1} using the method described previously.[3c] To assist the ^{13}C NMR and FT-IR characterization of the polymer-supported intermediates, aldehyde **10** was selected as a solution model,[3c] which also allowed a direct comparison of the reaction yields and diastereoselectivities.

In initial studies, aldehyde **9** was allowed to react with the (*E*)-enol dicyclohexylborinate **11** (5 equiv), derived from the dipropionate reagent (*R*)-**4a**,[8, 9] by shaking in Et_2O to form the *anti*–*anti* isomer **12** after oxidative boron removal. A loading of 0.51 mmol g^{-1} (i.e. 68% yield of isolated product) was determined by subsequent cleavage from the resin with HF/pyridine, leading to generation of the diol **13** with similarly high diastereoselectivity ($\geq 97\%$ *ds*) to that in the solution-phase reaction with **10**. An essentially quantitative conversion of **9** to **12** could be obtained, as determined by ^{13}C NMR analysis and cleavage to give **13** in 98% yield, by adopting a two-cycle protocol. Thus, 20 h after the first addition of enolate **11**, the resin was washed with Et_2O and dried, fresh enolate solution was again added, then after a further 16 h an oxidative workup (H_2O_2, MeOH, DMF, pH 7 buffer) was performed, followed by a final washing and drying of the resulting resin **12**.

To achieve efficient *syn*-selective reduction on solid phase, a novel modification of the Narasaka reduction protocol[10] was developed. Treatment of the resin-supported ketone **12** with $(c\text{Hex})_2BCl$ and Et_3N regenerated the dicyclohexylboron aldolate,[11] which was reduced efficiently by $LiBH_4$ to give the 1,3-*syn*-diol **14**. Gratifyingly, through this sequence of aldol addition, reduction, and cleavage from the resin using tetrabutylammonium fluoride (TBAF), the triol **15** was obtained in excellent yield (98%) with high diastereoselectivity (95% *ds*), comparable to that obtained from **10** using solution-phase chemistry (91%, $\geq 97\%$ *ds*).

Diversification in the β-hydroxy ketone reduction step was achieved by using a complementary *anti*-selective protocol. We found that the Evans–Tishchenko reduction[12] can be adapted successfully to solid phase, provided SmI_2 is employed stoichiometrically to achieve complete conversion. In this way, the ester **16** was prepared with $\geq 97\%$ *ds*, which gave the corresponding 1,3-*anti*-diol on reaction with $LiBH_4$.

Having installed four stereocenters on the growing chain anchored to the resin support, some functional group



Scheme 3. Solid-phase synthesis of aldehydes **18** and **20** from **9** (loading = 0.75 mmol g^{-1}) using *anti*-aldol addition and *syn* or *anti* reductions. a) $i\text{Pr}_2NEt$, DMAP, CH_2Cl_2, 20 °C, 48 h; b) O_3, CH_2Cl_2, −78 °C; Ph_3P, 20 °C, sonication, 16 h; c) $(c\text{Hex})_2BCl$, Et_3N, Et_2O, 0 °C, 4 h; d) 1) **11**, Et_2O, −78 → 0 °C, 20 h; filter and wash (two cycles); 2) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, 0 °C, 1 h; e) HF/py, py, MeCN, 20 °C, 16 h; f) 1) $(c\text{Hex})_2BCl$, Et_3N, Et_2O, 0 °C, 4 h; 2) $LiBH_4$, Et_3N, −78 °C, 4 h; 3) H_2O_2 (30% aq), MeOH, NaOH (10% aq), CH_2Cl_2, 20 °C, 16 h; g) TBAF, THF, 20 °C, 4 h; h) EtCHO, SmI_2, THF, −10 → 0 °C, 20 h; i) $(MeO)_2CMe_2$ or $MeOC(Me)=CH_2$, CSA, CH_2Cl_2, 20 °C, 48 h; j) DDQ, pH 7 buffer/CH_2Cl_2 (20/1), 20 °C, 3 h; k) py · SO_3, DMSO, Et_3N, CH_2Cl_2, 0 °C, 6 h; l) $LiBH_4$, THF, −78 → 20 °C, 16 h. *c*Hex = cyclohexyl, CSA = camphorsulfonic acid, DMF = *N*,*N*-dimethylformamide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-(*N*,*N*-dimethylamino)-pyridine, DMSO = dimethyl sulfoxide, py = pyridine.

manipulation was now required to regenerate the aldehyde functionality, thus enabling access to extended polyketide sequences. These transformations were selected to be compatible with the resin support and orthogonal to the silyl linker.[13] First, the diol **14** was converted into the *syn*-acetonide **17**, which had the expected ^{13}C NMR resonances ($\delta = 97.6$, 30.0, and 19.5).[14] The aldehyde was then introduced by deprotection of the PMB ether using DDQ,[15] followed by Parikh–Doering oxidation[16] using py · SO_3 and DMSO to

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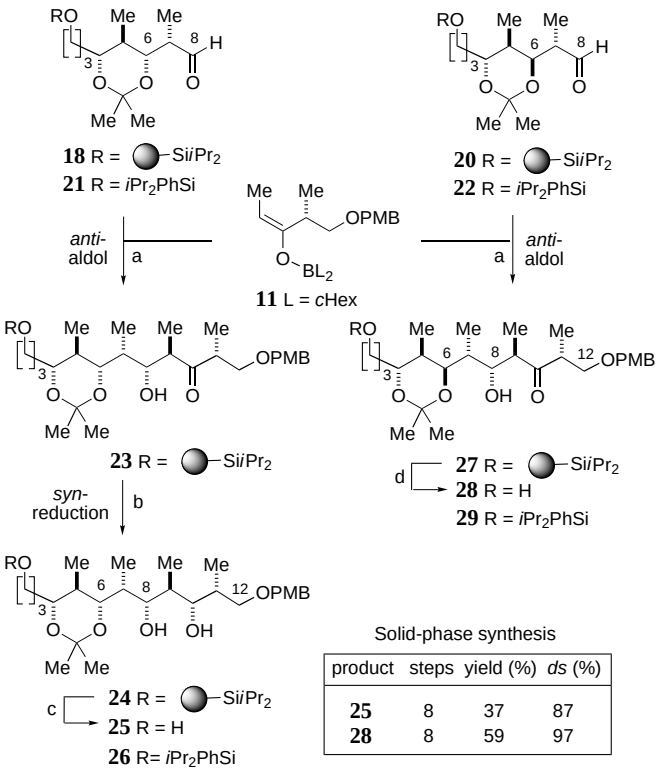
give **18**, which displayed a single, distinct, carbonyl resonance signal ($\delta = 204.1$). Similarly, the formation of the *anti*-acetonide **19** on the resin was confirmed by the diagnostic ^{13}C NMR resonances ($\delta = 100.4$, 24.7, and 23.6),[14] which was then taken on to the aldehyde **20** by PMB ether deprotection and oxidation.

As shown in Scheme 4, a second iteration of aldol chain extension was next performed on the solid-supported aldehydes **18** and **20**. For comparison purposes, the solution models **21** and **22** were also employed. The aldol addition



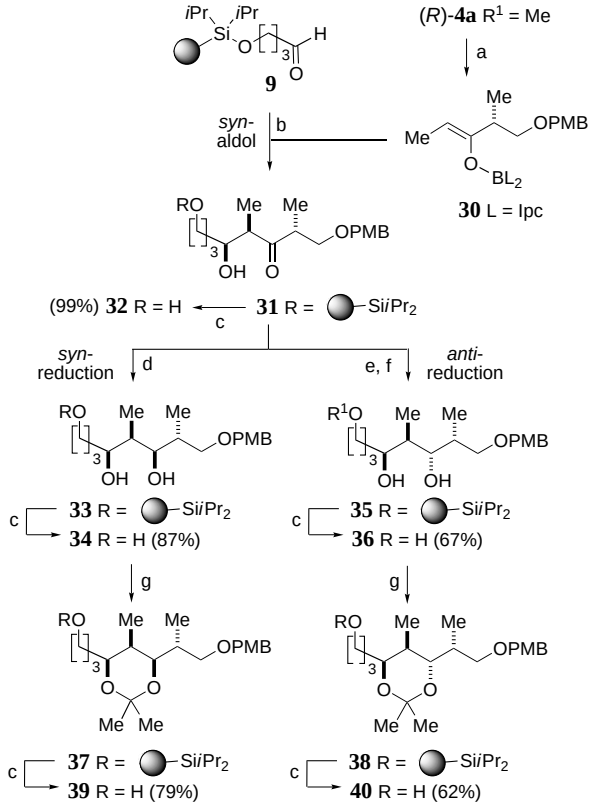
Solid-phase synthesis

product	steps	yield (%)	*ds* (%)
25	8	37	87
28	8	59	97

Scheme 4. Second iteration on solid phase, leading to long-chain polyketide sequences **25** and **28**. a) 1) **11**, Et_2O, $-78 \rightarrow 26\,^\circ C$, 16 h (two cycles); 2) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, $0\,^\circ C$, 1 h; b) 1) $(cHex)_2BCl$, Et_3N, Et_2O, $0\,^\circ C$, 4 h; 2) $LiBH_4$, Et_3N, $-78\,^\circ C$, 4 h; 3) H_2O_2 (30% aq), NaOH (10% aq), MeOH, CH_2Cl_2, $20\,^\circ C$, 16 h; c) TBAF, THF, $20\,^\circ C$, 16 h; d) HF/py, py, MeCN, $20\,^\circ C$, 16 h.

(two cycles) using the (*E*)-enolate **11** generated the ketone **23**, which was subjected to the *syn*-reduction protocol to give the 1,3-diol **24**. Cleavage from the solid support with HF/pyridine then gave the triol **25** with eight contiguous stereocenters,[17] which was isolated in 37% overall yield from **9** with 87% *ds*. This represents an average yield of 88% for each of the eight steps performed on the resin. A similar aldol addition with the C_6-epimeric aldehyde **20** generated the ketone **27**, which was cleaved to give the diol **28**[17] in 59% overall yield and 97% *ds*. Overall, this corresponds to an average yield of 94% for the eight steps performed on the solid support, which is markedly better than that achieved in solution where chromatographic purification from reagent by-products was required. In comparison, a 37% yield of **29** was obtained for the conventional solution-phase synthesis from **10** via **22**. Taken together, these findings demonstrate the efficiency of this solid-phase approach for polyketide synthesis. Potentially, further iteration should provide elaborate polyketide sequences with 12 or more contiguous stereocenters.[3d]

Polyketide diversity can also be realized through performing other stereochemical permutations during chain growth (Scheme 5). For example, *syn*-aldol additions can be achieved



Scheme 5. Solid-phase synthesis of stereotetrad alcohols **39** and **40** using *syn*-selective aldol addition with *anti* or *syn* reductions. a) (+)-Ipc_2BOTf, iPr_2NEt, CH_2Cl_2, $-78 \rightarrow 0\,^\circ C$, 4 h; b) 1) **30** (7 equiv), CH_2Cl_2, $-78 \rightarrow -26\,^\circ C$, 20 h, filter and wash (three cycles); 2) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, $20\,^\circ C$, 3 h; $-26\,^\circ C$, 16 h; c) HF/py, py, MeCN, $0 \rightarrow 20\,^\circ C$, 16 h (two cycles); d) 1) $(cHex)_2BCl$, Et_3N, Et_2O, $0\,^\circ C$, 4 h; 2) $LiBH_4$, $-78\,^\circ C$, 4 h; 3) H_2O_2 (30% aq), MeOH, DMF, pH 7 buffer, $20\,^\circ C$, 6 h, $-26\,^\circ C$, 16 h; e) EtCHO, SmI_2, THF, $-10 \rightarrow 0\,^\circ C$, 20 h; f) $LiBH_4$, $-78 \rightarrow 20\,^\circ C$, 20 h; g) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, $20\,^\circ C$, 2 d. Ipc = isopinocampheyl.

by using the (*Z*)-enol diisopinocampheyl borinate **30**, obtained by enolization of (*R*)-**4a** with (+)-Ipc_2BOTf/iPr_2-NEt.[8b, 18] Thus reaction of enolate **30** (two cycles) with the starting aldehyde **9** gave the *syn*–*anti* adduct **31**. Cleavage from the resin gave diol **32** in 87% yield and $\geq 95\%$ *ds*. Complete conversion can be achieved by carrying out a third cycle of enolate addition (giving a 99% yield of **32**). Remarkably, this aldol addition was found to be more stereoselective than the analogous solution-phase reaction performed on aldehyde **10** (91% *ds*). As in the *anti*-aldol series, reduction of **31** by $LiBH_4$ via the dicyclohexylboron aldolate gave the 1,3-*syn*-diol **33** (cleavage from the resin gave triol **34** in 87% yield and $\geq 95\%$ *ds*), while reduction using SmI_2/EtCHO, followed by treatment with $LiBH_4$, generated the corresponding 1,3-*anti*-diol **35** (cleavage from the resin gave triol **36** in 67% yield and 92% *ds*).[19] Transformation of

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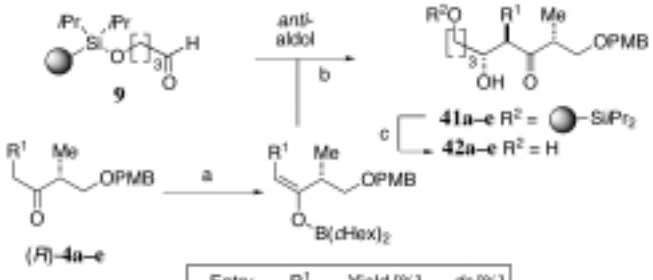
these 1,3-diols into the corresponding acetonides **37** and **38** allowed characterization by ^{13}C gel-phase NMR spectroscopy.[14] Subsequent cleavage from the resin led to the isolation of the stereochemically pure alcohols **39** (79%) and **40** (62%) after chromatography. Since the enantiomeric ketone (*S*)-**4a** and (−)-Ipc$_2$BOTf are available, it should be possible to access 12 out of the 16 possible stereotetrads per iteration with high diastereoselectivity.[20]

Finally, having demonstrated stereochemical permutations in the aldol addition and reduction steps, the introduction of further diversity by combinatorial variation of the chain extension reagent was addressed (Scheme 6). Five different



Entry	R^1	Yield [%]	*ds* [%]
a	Me	98	≥97
b	Et	95	≥97
c	*i*Pr	77	≥97
d	BnO	68	90
e	CH=CH$_2$	60	97

Scheme 6. Solid-phase synthesis of a library of β-hydroxy ketones **42a–e**. a) (*c*Hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 °C (−78 °C for **4d**), 4 h; b) 1) Et$_2$O, −78 → 26 °C, 16 h (two cycles); 2) H$_2$O$_2$ (30% aq), MeOH, DMF, pH 7 buffer, 0 °C, 16 h; c) HF/py, py, MeCN, 20 °C, 16 h.

ketones (*R*)-**4a–e** (R^1 = Me, Et, *i*Pr, BnO, CH=CH$_2$, respectively)[21] were chosen for library generation. Resin **9** was split into batches, to which each was added a different boron enolate, and two cycles of enolate addition were performed. After oxidative workup, cleavage of the resin-supported adducts **41a–e** with HF/pyridine gave the *anti*-configured β-hydroxy ketones **42a–e** with high diastereoselectivity.

In conclusion, we have demonstrated that boron-mediated aldol reactions of the chiral ketones **4** can be used for the efficient, solid-phase synthesis of novel polyketide-type sequences. Notably, better yields and comparable diastereoselectivities can usually be achieved in comparison with the conventional solution-phase reactions, which opens up the possibility of automation. While this approach mimics the processive mechanism of chain growth operating in the biosynthesis of polyketides, it enables much greater structural and stereochemical diversification through variation of the chain extension reagents, as well as in the stereochemistry of the aldol and reduction steps. In principle, a large variety of starter units,[7] immobilized on a solid support, and a wide range of chain extending units can be employed in a combinatorial fashion, leading to large, structurally diverse, libraries of polyketide-type sequences. Thus, this approach complements the combinatorial generation of new polyketide structures based on the genetically engineered reconstruction of biosynthetic pathways.[5]

Experimental Section

Representative procedure for *anti*-aldol reaction of **4a** with resin **9**:[3c] To a cooled solution (0 °C) of (*c*Hex)$_2$BCl (1.80 mL, 8.5 mmol) in dry Et$_2$O (23 mL) under Ar was added Et$_3$N (1.25 mL, 9.0 mmol). After 10 min (*R*)-**4a** (1.18 g, 5.0 mmol) was added and the reaction mixture stirred for a further 4 h. The resulting solution of enolate **11** was added by cannula to the resin **9** (1.0 g) cooled to −78 °C and shaking was maintained for 1 h, before storing in the freezer (−26 °C, 16 h). After shaking for a further 4 h at 0 °C, the enolate solution was filtered off and the resin washed with Et$_2$O and dried under reduced pressure. A second cycle was then carried out. To the resin cooled to −78 °C, a solution of enolate **11**, prepared as above, was added and shaking was maintained for 1 h, before storing in the freezer (−26 °C, 16 h). The resin was filtered and washed sequentially with pH 7 buffer, H$_2$O, H$_2$O/THF, THF, and MeOH. To the resin at 0 °C were added DMF (4 mL), MeOH (2 mL), pH 7 buffer (4 mL), and H$_2$O$_2$ (30%; 12 mL) and shaking was continued for 1 h before storing in the freezer (−26 °C) for 16 h. After filtering, the resin was washed with H$_2$O, H$_2$O/THF, THF, CH$_2$Cl$_2$, and MeOH and dried under reduced pressure at 50 °C for 3 h. This gave the pale yellow resin **12**. IR (KBr disk): $\tilde{\nu}$ = 3440, 1708, 1098 cm^{-1}; ^{13}C NMR (100.6 MHz, CD$_2$Cl$_2$): δ = 217.8, 159.4, 130.2, 129.4, 113.8, 73.5, 73.0, 72.3, 64.0, 55.3, 52.2, 45.8, 31.3, 29.1, 17.4, 13.6, 13.4, 12.6, 12.2.

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[17] The stereochemistry was established using the methods described previously (ref. [3d]). **25**: $[\alpha]_D^{25} = -1.8$ ($c = 0.87$, $CHCl_3$); IR (thin film): $\tilde{\nu} = 3442, 3019, 1513, 1466, 1383, 1248\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 4.78 (s, 1H), 4.46 (ABq, 2H), 4.13 (s br, 1H), 3.80 (s, 3H), 3.76–3.72 (m, 3H), 3.64 (t, $J = 5.9$ Hz, 2H), 3.58 (dd, $J = 8.7$, 6.9 Hz, 1H), 3.53 (td, $J = 8.7$, 1.9 Hz, 1H), 3.37 (dd, $J = 8.7$, 6.9 Hz, 1H), 2.10 (s br, 1H), 2.00–1.95 (m, 2H), 1.84–1.79 (m, 1H), 1.75–1.55 (m, 5H), 1.48 (s, 3H), 1.37 (s, 3H), 0.93 (d, $J = 7.1$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.77 (d, $J = 6.6$ Hz, 3H), 0.72 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 159.0, 131.0, 129.2, 113.7, 98.3, 83.4, 81.0, 76.0, 74.3, 72.9, 63.0, 55.3, 38.1, 35.9, 34.9, 34.1, 29.9, 29.6, 28.4, 19.8, 13.1, 11.8, 9.4, 4.8$; HRMS (CI): calcd for $C_{27}H_{47}O_7$ $[M+H^+]$ 483.3322; found: 483.3321. **28**: $[\alpha]_D^{25} = -5.6$ ($c = 1.06$, $CHCl_3$); IR (thin film): $\tilde{\nu} = 3415, 2934, 1709, 1611, 1513, 1458\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.20$ (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.39 (ABq, 2H), 4.20 (dd, $J = 9.7$, 2.3 Hz, 1H), 3.79 (s, 3H), 3.82–3.78 (m, 1H), 3.65 (t, $J = 8.9$ Hz, 1H), 3.65–3.60 (m, 2H), 3.38 (dd, $J = 8.9$, 4.6 Hz, 1H), 3.23 (td, $J = 7.5$, 2.5 Hz, 1H), 3.10 (m, 1H), 2.82 (m, 1H), 2.69 (d, $J = 4.7$ Hz, 1H), 2.34 (s br, 1H), 1.75–1.50 (m, 6H), 1.32 (s, 3H), 1.25 (s, 3H), 1.03 (d, $J = 7.1$ Hz, 3H), 1.00 (d, $J = 7.3$ Hz, 3H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 217.5, 159.3, 129.6, 129.3, 113.8, 101.0, 75.5, 73.0, 72.2, 70.3, 69.1, 62.7, 55.2, 50.5, 44.3, 38.4, 33.8, 31.5, 29.7, 24.8, 23.7, 14.2, 12.8, 11.7, 7.9$; HRMS $[ES^+]$: calcd for $C_{27}H_{44}O_7Na$ $[M+Na]$ 503.2973; found: 503.2963.
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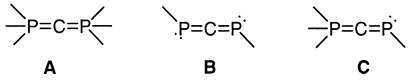
Synthesis, Structure, and Reactivity of a $1\sigma^4,3\sigma^2$-Diphosphaallene**

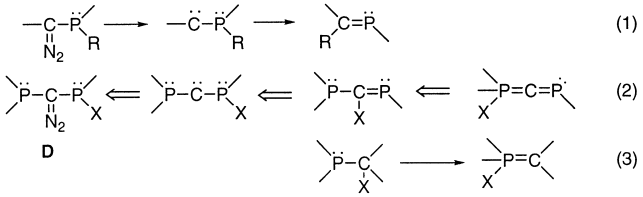
Tsuyoshi Kato, Heinz Gornitzka, Antoine Baceiredo, and Guy Bertrand*

Among the possible heterocumulenes featuring the PCP sequence, $1\sigma^4,3\sigma^4$-diphosphaallenes (carbodiphosphoranes) **A**[1] and $1\sigma^2,3\sigma^2$-diphosphaallenes **B**[2] have been known for many years. Here we report the synthesis of a $1\sigma^4,3\sigma^2$-diphosphaallene **C**. Such a highly functionalized molecule

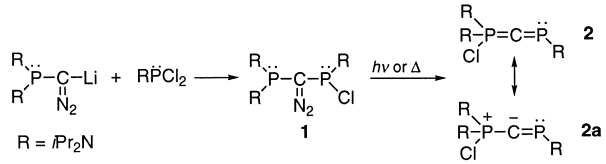


(two different types of phosphorus–carbon "double" bond and a lone pair at one of the phosphorus atoms) has only been postulated as an intermediate, but never observed spectroscopically.[3]

Our synthetic strategy was based on two consecutive rearrangements: the well-established 1,2-migration reaction of singlet carbenes,[4] which operates for phosphinocarbenes [Eq. (1)],[5] and the 1,2-halogen shift associated with α-halogenophosphanes [Eq. (3)].[6] Combining these two 1,2-migration reactions, a possible precursor for the preparation of the desired $1\sigma^4,3\sigma^2$-diphosphaallene can be identified as the (phosphino)(chlorophosphino)diazomethane of type **D** [Eq. (2)].



Exactly this type of derivative, namely [bis(diisopropylamino)phosphino][chloro(diisopropylamino)phosphino]diazomethane (**1**), is readily available in one step by addition of the lithium salt of [bis(diisopropylamino)phosphino]diazomethane[7] to dichloro(diisopropylamino)phosphane (Scheme 1).



Scheme 1.

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