

# A Practical Building Block for the Synthesis of Discodermolide

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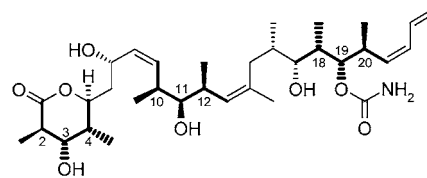
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## Abstract:

A new highly diastereoselective and practical route to the lactone **6a** which is used as a key building block for the total synthesis of the microtubule-stabilizing anticancer agent discodermolide is reported. This exploits the chiral auxiliary (4*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**7**) which conveys crystallinity to the synthetic intermediates throughout the entire process. Purifications can thus be performed by recrystallization, avoiding chromatography to afford the final product in high enantiomeric purity. The overall efficiency is augmented by the facile recovery of the auxiliary by precipitation at the end of the sequence.

## Introduction

Discodermolide (**1**) is a marine polyketide discovered by Gunasekera and co-workers at the Harbor Branch Oceanographic Institution in 1990 and is isolated from a rare caribbean deep-sea sponge *Discodermia dissoluta*.<sup>1</sup> Discodermolide is now recognized as a member of a group of antimetabolic agents including Taxol (paclitaxel), known to act by microtubule stabilization.<sup>2</sup> The highly encouraging biological profile of discodermolide makes it a promising candidate for clinical development as a chemotherapeutic agent in oncology.<sup>3</sup> However, extensive exploration of the efficacy of this compound has initially been hampered by

discodermolide (**1**)

**Figure 1.**

the scarce supply of the material available from the natural source. The yield initially reported by Gunasekera in the isolation of discodermolide was 0.002% (w/w from frozen sponge). The supply problem has since been alleviated by recent progress in the total synthesis of discodermolide<sup>4</sup> which has culminated in the preparation of 1 g of material by Smith and co-workers<sup>4d,e</sup> and the report by Paterson and co-workers of two generations of practical syntheses.<sup>4k,m,n</sup> Accordingly, discodermolide is currently undergoing Phase I clinical trials sponsored by Novartis Pharma AG who licensed the compound from the Harbor Branch Oceanographic Institution in 1998 to develop it as an anticancer agent. Drug supply needs (60 g) have been met using total synthesis.<sup>4p</sup> However, to address the drug supply of more advanced clinical trials, further efforts in synthesis are necessary. Our interest for the development of a process for discodermolide revolved first around the efficient access to the recurring *anti-syn* stereochemical triad highlighted in Figure 1. The use of a common building block containing this motif results in a significant reduction of complexity in the total synthesis of discodermolide by diminishing the total number of steps.<sup>4c</sup>

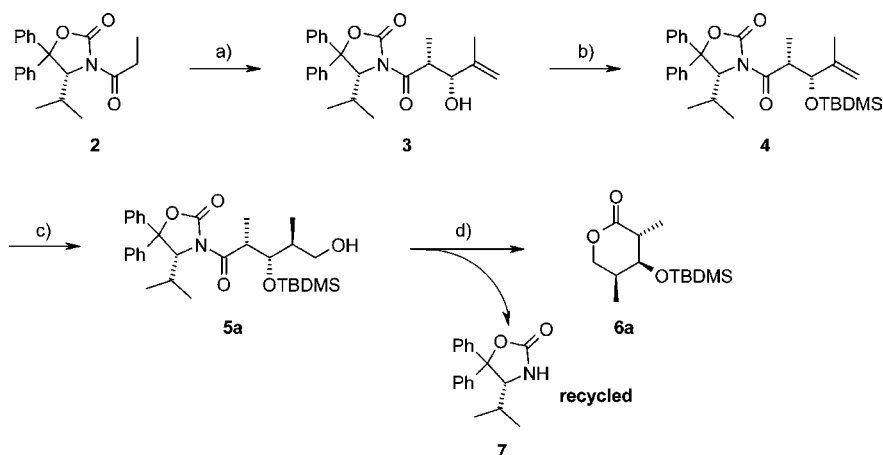
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Scheme 1<sup>a</sup>

<sup>a</sup> (a) *n*Bu<sub>3</sub>BOTf (1 equiv), Et<sub>3</sub>N (1.2 equiv), methacrolein (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to 0 °C, 2 h. (b) TBDMSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 0.5 h, 70% over two steps. (c) (i) 9-BBN (2 equiv), THF, 23 °C, 5 h; (ii) pH 7, H<sub>2</sub>O<sub>2</sub>, EtOH/THF, 23 °C, 15 h, 86%. (d) KO-*t*-Bu (2 mol %), THF, 0 °C, 1 h, quantitative.

## Results and Discussion

We selected the known lactone **6a** containing the correct triad of contiguous stereocenters present in discodermolide as our common building block.<sup>5</sup> The critical role of this common fragment required development of a route amenable to large-scale production.<sup>6</sup> Whereas syntheses of **6a** are reported, their adaptation to a production process remains problematic in terms of length and chromatographic purifications.<sup>7</sup> To control stereochemistry, we chose as point of departure the Evans *syn*-boron aldol protocol enlisting the inexpensive methacrolein and the known acylated oxazolidinone **2** (Scheme 1).<sup>8a,b</sup> We anticipated that the presence of the second generation auxiliary (4*R*)-4-isopropyl-5,5-diphenyloxazolidin-2-one (**7**) developed by Seebach would confer high crystallinity to the intermediates throughout the route toward **6a** thus providing a practical advantage for isolation and purifications.<sup>9</sup>

Aldol coupling followed by TBDMS-silylation gave the crystalline intermediate **4** as a single diastereomer in 70% yield over two steps. Hydroboration of the alkene moiety in **4** with 9-BBN then afforded the expected *anti*-product **5a** as a single diastereomer.<sup>10</sup> Finally, lactonization, best performed by treatment of **5a** with a catalytic amount of *t*-BuOK, provided **6a** as a solid in quantitative yield. Isolation of **6a** was facilitated by removal of the recyclable oxazolidinone auxiliary through quantitative crystallization from the

reaction mixture. Hence, a simple filtration provided analytically pure lactone **6a**. The overall yield for the discodermolide common building block was 60% (based on **2**).

Whereas this synthesis of **6a** provided us with a proof of concept, demonstrating the high crystallinity of all the oxazolidinone-containing intermediates as well as the ease of recycling of the auxiliary and supplied us with an initial multigram amount of material to pursue on our synthesis of discodermolide, it was associated with a number of problems. The range of the protecting group for the C<sub>3</sub>-OH function that could be introduced at the stage of the derivative **3** was somewhat limited. Specifically, PMB was installed with moderate yield, even by using *p*-methoxybenzyl-trichloroacetimidate (PMBOC(=NH)CCl<sub>3</sub>) and a series of acid catalysts. More importantly, the TES-protected lactone **6b** (Scheme 2), a variation needed downstream in the synthesis, could not be accessed through our route. Indeed, the TES group when installed after the boron aldol underwent partial cleavage during the hydroboration step. Furthermore, 9-BBN caused difficulties as the 1,5-cyclooctanediol resulting from oxidative workup precluded the crystallization of the solid alcohol **5a** and a chromatography was required for purification.

To address these obstacles and gain in flexibility for alternative protecting groups, we modified our route as shown in Scheme 2. The aldol product **3** was hydroborated directly prior to silylation. Whereas disiamylborane as an alternative to 9-BBN proved ineffective in terms of conversion and BH<sub>3</sub>•DMS resulted in partial cleavage of the auxiliary during reaction, thexylborane, which is converted to volatile 2,3-dimethyl-butane-2-ol after oxidative workup, allowed direct crystallization of the diol **8** in 84% yield from the reaction mixture thus avoiding chromatographic purification. Thexylborane showed the same diastereoselectivity as 9-BBN, and only the desired *anti*-diastereomer could be observed in the hydroboration. Strong chelation of boric acid by the diol **8** caused problems in the purification step at the beginning, but this could be circumvented by treatment of the crude diol **8** prior to recrystallization with aqueous NaOH, at pH < 11 to avoid spontaneous lactonization to **6c**.

(5) Koch, G.; Loiseleur, O. Patent No. 0257251 WO, July 25, 2002.

(6) A related approach has been reported independently by Day and co-workers: Day, B. W.; Kangani, C. O.; Avor, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1161.

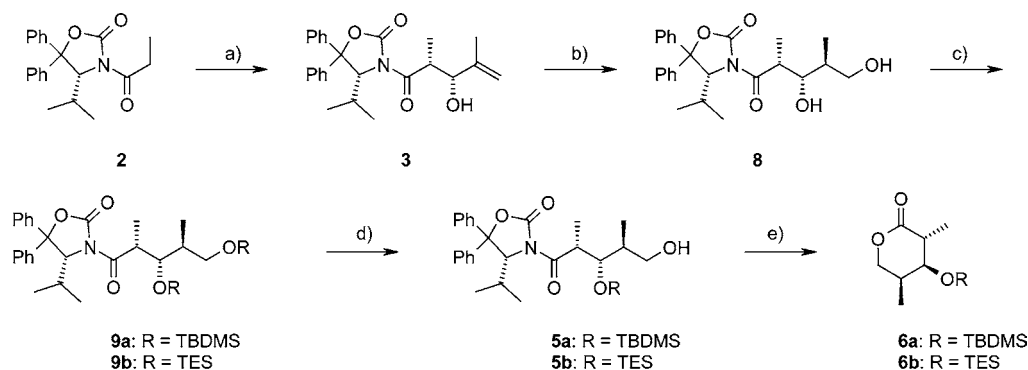
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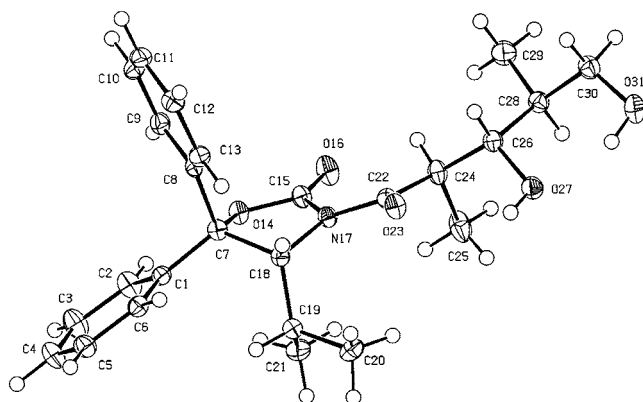
(9) The propensity of **7** and its enantiomer to give crystalline derivatives has been reported independently by Hintermann and Seebach and Gibson and co-worker.<sup>8a,c</sup> For a convenient preparation of **7**, see ref 8b. Both enantiomers of the auxiliary are commercially available (Aldrich, Shiratori Pharmaceuticals Co. Ltd., Japan and Onyx Scientific Ltd. UK).

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## Scheme 2<sup>a</sup>



<sup>a</sup> (a) Bu<sub>2</sub>-BOTf (1 equiv), Et<sub>3</sub>N (1.3 equiv), methacrolein (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C to 0 °C, 2 h, 74%. (b) (i) hexylborane (1.7 equiv), 0 °C, 2 h; (ii) pH 7, H<sub>2</sub>O<sub>2</sub>, EtOH/THF, 23 °C, 14 h, 84%. (c) **9a**: TBDMSOTf (2.1 equiv), 2,6-lutidine (2.5 equiv), 0 °C, 2.0 h. **9b**: TESCl (2.1 equiv), imidazole (2.4 equiv), DMAP (10 mol %), DMF, 40 °C, 2 h. (d) **5a**: Cl<sub>2</sub>CCO<sub>2</sub>H, MeOH, 0 °C, 1.75 h. **5b**: AcOH, THF/MeOH/H<sub>2</sub>O 5:5:1, 0 °C, 5 h, 72% over two steps. (e) KO-*t*-Bu (2 mol %), THF, 0 °C, 0.5 h. **6a**: 88% over three steps. **6b**: 95%.



**Figure 2.** Structure of **8** in the crystal.<sup>14</sup> Atomic displacement ellipsoids drawn at the 50% probability level, hydrogen atoms drawn as spheres of arbitrary radius. Stereochemistry: C18R, C24R, C26S, C28S. Flack *x* refined to 0.01(11).

Silylation of **8** with TBDMSOTf followed by deprotection of the primary hydroxyl group and lactonization provided **6a** in 55% overall yield (based on **2**). The TES-lactone **6b** was obtained in 43% overall yield. Both **6a** and **6b** were purified by distillation under high vacuum. Potential spontaneous lactonization upon shelf storage of alcohols **8**, **5a**, and **5b** to give respectively **6c**, **6a**, and **6b** was precluded by the fact that these compounds are crystalline. These efficient five-step sequences can be performed routinely on a 100 g scale without any chromatography. In contrast to the approaches adopted by other groups,<sup>4</sup> the synthesis of our common building block does not make use of the expensive methyl (*S*)-2-methyl-3-hydroxypropionate (Roche ester) as a starting material. The stereochemistry is dictated by the readily recovered oxazolidinone **7** instead, which augments the efficiency of the procedure. The configurations of **6a** and **6b** were confirmed by single-crystal X-ray diffraction of the precursor **8** (Figure 2) as well as by comparison of the analytical data of **6a** with a sample of lactone prepared in our lab according to a published procedure.<sup>7a</sup>

Ring-opening of **6a** as the initial step for further elaborations toward the key fragments necessary for the synthesis of discodermolide was investigated next. We first converted

the lactone to the lactol **10** as a mixture of anomers (ca. 4:1) by DIBAL-H reduction and intended to take advantage of the masked aldehyde to install the trisubstituted C<sub>13</sub>-C<sub>14</sub> double bond present in discodermolide (Figure 1) via a Still-Gennari olefination (Scheme 3, **11**).<sup>11</sup>

However, **10** proved to be unreactive to the standard reaction conditions. The direct conversion of the lactone to the olefin by using a protocol developed by Takacs and co-workers was unsuccessful as well.<sup>12</sup> Standard Wittig conditions used in a test reaction did provide olefination product, but this was accompanied by extensive  $\alpha,\beta$ -elimination of silanol to give **12**. Likewise, attempted conversion of **6a** to the TBDMS- or acetate-protected hydroxyaldehyde only resulted in silylation or acetylation of the anomeric hydroxyl group to give **13a** and **13b**. With the lactol proving to be reluctant to undergo ring-opening,<sup>13</sup> we turned our attention on the reactivity of the lactone and found that it could reproducibly be converted to the corresponding Weinreb amide **14** providing a convenient starting point for further synthetic elaboration (Scheme 4).

## Conclusion

In conclusion, we have reported the practical preparation of the lactone **6a** chosen as a common building block for the synthesis of discodermolide, a promising anti-cancer drug candidate currently in Phase I clinical trials. We have chosen a strategy which makes use of the easily recyclable oxazolidinone **7** to control stereochemistry efficiently, to impart crystallinity to the intermediates throughout the process, and to avoid the costly Roche ester. The elaboration of **6a** to key fragments of discodermolide and their coupling is presently subject to a patent application and will be reported in due course.

## Experimental Section

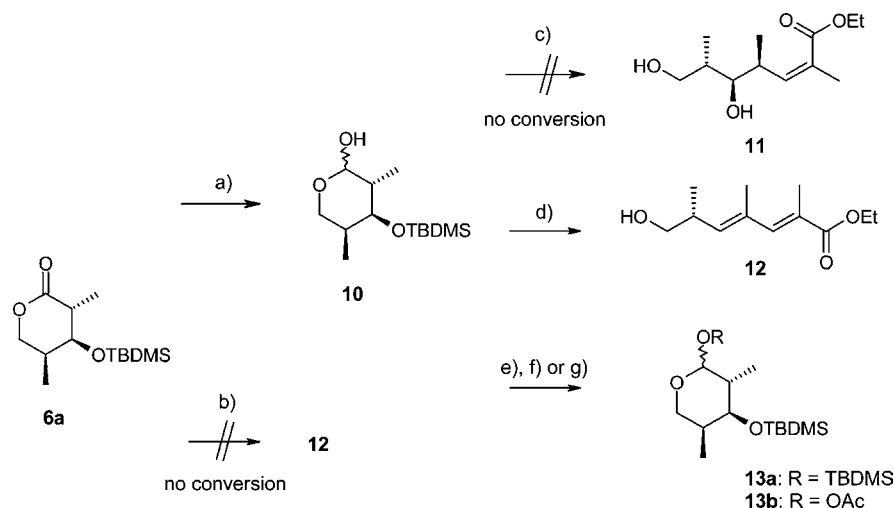
**(R)-3-[(2R,3R)-3-Hydroxy-2,4-dimethyl-pent-4-enyl]-4-isopropyl-5,5-diphenyl-oxazolidin-2-one (3).** A solution

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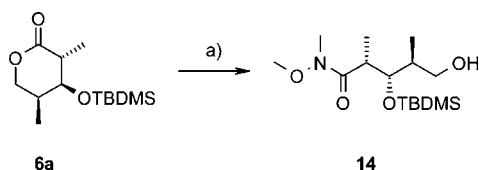
(13) An indirect solution for a similar case has since been reported by Tholander and Carreira: Tholander, J.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 613.

**Scheme 3<sup>a</sup>**



<sup>a</sup> (a) DIBAL-H, THF,  $-78^{\circ}$ , 96%. (b) DIBAL-H,  $(\text{CF}_3\text{CH}_2\text{O})\text{P}(\text{O})\text{CH}(\text{CH}_3)\text{CO}_2\text{Et}$ , KHMDS, 18-crown-6, THF. (c)  $(\text{CF}_3\text{CH}_2\text{O})\text{P}(\text{O})\text{CH}(\text{CH}_3)\text{CO}_2\text{Et}$ , KHMDS, 18-crown-6, THF. (d)  $[(\text{C}_6\text{H}_5)_3\text{PCH}(\text{CH}_3)\text{CO}_2\text{Et}]^+\text{Br}^-$ , BuLi, THF. (e) TBDMSOTf,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ . (f) TBDMSOCl, imidazole, DMAP, DMF. (g)  $\text{Ac}_2\text{O}$ , pyridine, DMAP.

**Scheme 4<sup>a</sup>**



<sup>a</sup> (a) *i*PrMgCl (3 equiv),  $\text{HN}(\text{OMe})\text{Me}\cdot\text{HCl}$  (1.6 equiv), THF,  $-15^{\circ}\text{C}$ , 1.5 h, 98%.

of **2** (20.2 g, 60 mmol) in 80 mL of  $\text{CH}_2\text{Cl}_2$  under an atmosphere of argon was treated sequentially at  $0^{\circ}\text{C}$  with a 1.0 M solution of *n*-Bu<sub>2</sub>BOTf in  $\text{CH}_2\text{Cl}_2$  (60 mL, 60 mmol) and triethylamine (7.6 g, 75 mmol). After stirring at  $0^{\circ}\text{C}$  for 1 h, the resulting solution was cooled to  $-78^{\circ}\text{C}$ . Methacrolein (12.6 g, 180 mmol) dissolved in 20 mL of  $\text{CH}_2\text{Cl}_2$  was then added. The reaction mixture was stirred successively at  $-78^{\circ}\text{C}$  for 1 h and at  $-45^{\circ}\text{C}$  for 1 h. Water (80 mL) was added at  $0^{\circ}\text{C}$ . The phases were separated, and the organic layer was treated sequentially at  $0^{\circ}\text{C}$  with phosphate buffer (pH 7, 80 mL) and 35%  $\text{H}_2\text{O}_2$  (10 mL). After stirring for 30 min at ambient temperature, the layers were separated. The organic layer was washed with 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$  (2  $\times$  80 mL) and brine (80 mL), dried over  $\text{MgSO}_4$ , and concentrated in vacuo to give 34.2 g of the crude alcohol **3** as a slightly yellowish crystalline material. Purification by recrystallization in heptane afforded 18.1 g (74%) of product as colorless crystals: mp  $99.5$ – $100.0^{\circ}\text{C}$ ;  $R_f = 0.27$  (SiO<sub>2</sub>, 3:1 heptane–AcOEt); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz, 300 K)  $\delta$  7.62 (d,  $J = 8.4$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.56 (d,  $J = 7.6$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.45–7.28 (two m, 6H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 6.91 (d,  $J = 2.8$  Hz, 1H, C<sub>4</sub>–H), 4.93 (d,  $J = 5.6$  Hz, 1H, C<sub>3</sub>–OH), 4.32 (s, 1H, C<sub>5</sub>–H<sub>a</sub>), 4.03 (q,  $J = 1.6$  Hz, 1H, C<sub>5</sub>–H<sub>b</sub>), 3.85 (dd,  $J = 9.2$ , 5.2 Hz, 1H, C<sub>3</sub>–H), 3.78 (qd,  $J = 9.2$ , 6.4 Hz, 1H, C<sub>2</sub>–H), 2.05 (qqd,  $J = 7.2$ , 6.8, 2.8 Hz, 1H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 1.22 (d,  $J = 6.4$  Hz, 3H, C<sub>2</sub>–CH<sub>3</sub>), 1.17 (s, 3H, C<sub>4</sub>–CH<sub>3</sub>), 0.88 (d,  $J = 7.2$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.64 (d,  $J = 6.8$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>); <sup>13</sup>C NMR (CD<sub>3</sub>OD, 125 MHz, 300 K):  $\delta$  176.1, 154.3, 147.4, 145.0, 140.1, 130.6, 130.3, 130.1, 129.7, 127.2,

126.8, 113.4, 90.4, 77.2, 66.3, 43.2, 31.4, 23.3, 19.0, 17.6, 17.1; IR (KBr)  $\nu_{\text{max}}$  3512m, 2966m, 1768s, 1687s, 1451m, 1363s, 1320m, 1209s, 1182m, 1052m, 994m, 949m, 910m, 761m, 705m  $\text{cm}^{-1}$ ; MS (ES<sup>+</sup>)  $m/z$  (%) 837 (34, [2 M + Na]<sup>+</sup>), 631 (100, [3 M + Ca]<sup>2+</sup>), 623 (100, [2 M + Na + H]<sup>2+</sup>), 430 (65, [M + Na]<sup>+</sup>).

**(R)-3-[(2R,3S,4S)-3,5-Dihydroxy-2,4-dimethyl-pentanoyl]-4-isopropyl-5,5-diphenyl-oxazolidin-2-one (8)**. A solution of hexyl borane in THF [prepared in situ by dropwise addition at  $0^{\circ}\text{C}$  of 2,3-dimethyl-2-butene (37.2 g, 442 mmol) to  $\text{BH}_3\cdot\text{THF}$  (1 M in THF, 442 mL, 442 mmol) followed by 1 h stirring at  $0^{\circ}\text{C}$ ] at  $0^{\circ}\text{C}$  under an atmosphere of argon was treated dropwise over a period of 40 min with a solution of **3** (106 g, 260 mmol) in THF (100 mL). After stirring at  $0^{\circ}\text{C}$  for 2 h, the reaction mixture was treated sequentially and under temperature control (ca.  $0^{\circ}\text{C}$ ) with EtOH/THF 1:1 v/v (520 mL) over a period of 25 min, pH 7 phosphate buffer (520 mL) over a period of 15 min, and 35% aqueous hydrogen peroxide (250 mL) over a period of 20 min. Thereupon, the resulting solution was stirred successively at  $0^{\circ}\text{C}$  for 1 h and at  $23^{\circ}\text{C}$  for 14 h before being extracted twice with hexane (1500 mL and 1000 mL). The organic extracts were washed with  $\text{Na}_2\text{S}_2\text{O}_3$  (1000 mL and 600 mL) and pH 7 phosphate buffer (600 mL), combined, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo. The residue was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (1000 mL) and  $\text{H}_2\text{O}$  (600 mL), and the pH of the water layer of the resultant two-phase mixture was increased from 4.1 to 11.2 by dropwise addition monitored with a pH meter over a period of 1 h of 1 N NaOH (110 mL). After, the pH of the aqueous layer remained stable at 11.2 for 15 min, the layers were separated. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (250 mL). The organic extracts were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (300 mL) and saturated aqueous NaCl (300 mL), combined, dried ( $\text{MgSO}_4$ ), and concentrated in vacuo to give the crude diol (109.2 g) as colorless crystals. Purification by recrystallization in methylcyclohexane (1.3 L) afforded 92.8 g (84%) of diol **8** as colorless crystals: mp  $103.5$ –

104.5 °C;  $R_f = 0.27$  (SiO<sub>2</sub>, 1:1 heptane–AcOEt); <sup>1</sup>H NMR (DMSO, 400 MHz, 300 K)  $\delta$  7.61 (d,  $J = 7.6$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.55 (d,  $J = 7.5$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.48–7.20 (m, 6H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 5.53 (d,  $J = 2.5$  Hz, 1H, C<sub>4</sub>–H), 4.38 (d,  $J = 6.8$  Hz, 1H, C<sub>3</sub>–OH), 4.14 (t,  $J = 4.8$  Hz, 1H, C<sub>5</sub>–OH), 3.63 (dq,  $J = 7.2$ , 6.8 Hz, 1H, C<sub>2</sub>–H), 3.35–3.25 (ddd, 1H, C<sub>3</sub>–H, partially obscured by water), 3.11–3.06 (m, 1H, C<sub>5</sub>–H<sub>a</sub>), 3.00–2.95 (m, 1H, C<sub>5</sub>–H<sub>b</sub>), 2.10–1.98 (br qqd,  $J = 6.9$ , 6.7, 2.5 Hz, 1H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 1.14 (d,  $J = 6.8$  Hz, 3H, C<sub>2</sub>–CH<sub>3</sub>), 1.10–0.98 (br m, 1H, C<sub>4</sub>–H), 0.86 (d,  $J = 6.9$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.62 (d,  $J = 6.7$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.45 (d,  $J = 6.9$  Hz, 3H, C<sub>4</sub>–CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz, 300 K):  $\delta$  175.1, 152.5, 143.1, 138.2, 128.79, 128.76, 128.54, 128.51, 128.3, 127.8, 125.4, 125.3, 124.98, 124.95, 88.7, 73.6, 64.5, 63.2, 41.1, 39.0, 29.6, 21.4, 15.7, 14.6, 14.0; IR (KBr)  $\nu_{\max}$  3460m (br), 2966m, 1776s, 1707m, 1452m, 1362m, 1320w, 1245w, 1210m, 1178m, 1150w, 1052m, 1037m, 991m, 762m, 706m cm<sup>-1</sup>; MS (ES+)  $m/z$  (%) 873 (28, [2 M + Na]<sup>+</sup>), 658 (12, [3 M + Ca]<sup>2+</sup>), 448 (100, [M + Na]<sup>+</sup>), 445 (13, [2 M + Ca]<sup>2+</sup>).

**(R)-3-[(2R,3S,4S)-3,5-Bis(tert-butyl-dimethyl-silyloxy)-2,4-dimethyl-pentanoyl]-4-isopropyl-5,5-diphenyl-oxazolidin-2-one (9a).** To a solution of **8** (25.0 g, 59 mmol) and 2,6-lutidine (17 mL, 146 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (120 mL) at 0 °C under an atmosphere of argon TBDMSOTf (29 mL, 126 mmol) was added dropwise over a period of 10 min. After stirring at 0 °C for 2 h, the reaction mixture was worked up. Aqueous 1 N HCl (150 mL) was added dropwise at 0 °C over a period of 10 min followed by heptane (200 mL). The aqueous layer was extracted with heptane (100 mL). The organic extracts were combined, washed with saturated aqueous NaHCO<sub>3</sub> (200 mL) and saturated aqueous NaCl (200 mL), dried over MgSO<sub>4</sub>, and concentrated in vacuo to give 40 g of the crude bis-silyl ether **9a** as a colorless solid which did not require further purification. An analytical sample of **9a** was obtained by recrystallization in MeOH: colorless crystals; mp 104–105 °C;  $R_f = 0.66$  (SiO<sub>2</sub>, 1:1 heptane–AcOEt); <sup>1</sup>H NMR (DMSO, 400 MHz, 300 K)  $\delta$  7.67 (d,  $J = 8.0$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.58 (d,  $J = 7.9$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.42–7.20 (two m, 6H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 5.60 (d,  $J = 1.9$  Hz, 1H, C<sub>4</sub>–H), 3.90 (dd,  $J = 5.8$ , 4.0 Hz, 1H, C<sub>3</sub>–H), 3.73 (qd,  $J = 6.9$ , 5.8 Hz, 1H, C<sub>2</sub>–H), 3.19 (dd,  $J = 9.9$ , 6.5 Hz, 1H, C<sub>5</sub>–H<sub>a</sub>), 3.03 (dd,  $J = 9.9$ , 6.7 Hz, 1H, C<sub>5</sub>–H<sub>b</sub>), 2.08 (heptd,  $J = 6.7$ , 1.9 Hz, 1H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 1.41 (qddd,  $J = 7.0$ , 6.7, 6.5, 4.0 Hz, 1H, C<sub>4</sub>–H), 1.15 (d,  $J = 6.9$  Hz, 3H, C<sub>2</sub>–CH<sub>3</sub>), 0.87 (d,  $J = 6.7$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.83 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.80 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.61 (d,  $J = 6.7$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.56 (d,  $J = 7.0$  Hz, 3H, C<sub>4</sub>–CH<sub>3</sub>), –0.04 (s, 3H, SiCH<sub>3</sub>), –0.09 (s, 3H, SiCH<sub>3</sub>), –0.11 (s, 3H, SiCH<sub>3</sub>), –0.14 (s, 3H, SiCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz, 300 K)  $\delta$  175.5, 151.9, 142.0, 137.8, 128.5, 128.1, 127.9, 127.4, 125.4, 125.0, 88.5, 73.2, 64.2, 64.1, 41.9, 41.1, 29.6, 25.6, 25.5, 21.4, 17.9, 17.8, 15.8, 15.4, 13.5, –4.4, –4.6, –5.9; IR (KBr)  $\nu_{\max}$  2954m, 2928m, 1772s, 1712m, 1450m, 1363m, 1251m, 1209m, 1093m, 1055m, 861m, 838m, 776m, 759m, 704m cm<sup>-1</sup>; MS (ES+)  $m/z$  (%) 1000 (7, [3 M + Ca]<sup>2+</sup>), 676 (100, [M + Na]<sup>+</sup>), 673 (14, [2 M + Ca]<sup>2+</sup>), 654 (8, [M + H]<sup>+</sup>).

**(R)-3-[(2R,3S,4S)-3-(tert-Butyl-dimethyl-silyloxy)-5-hydroxy-2,4-dimethyl-pentanoyl]-4-isopropyl-5,5-diphenyl-oxazolidin-2-one (5a).** To a solution of crude **9a** (40 g) in MeOH (100 mL) at 0 °C was added dichloroacetic acid (38 g, 295 mmol). After stirring at 0 °C for 1 h and 45 min, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> (600 mL) and extracted with TBME (2 × 400 mL). The organic extracts were washed with saturated aqueous NaCl (400 mL), combined, dried (MgSO<sub>4</sub>), and concentrated in vacuo to provide the alcohol **5a** (39 g) as a colorless solid. This material was used in the next step without further purification.  $R_f = 0.59$  (SiO<sub>2</sub>, 1:1 heptane–AcOEt); <sup>1</sup>H NMR (DMSO, 500 MHz, 300 K)  $\delta$  7.66 (d,  $J = 7.8$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.58 (d,  $J = 7.8$  Hz, 2H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 7.42–7.20 (two m, 6H, C<sub>5</sub>–(C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>), 5.57 (d,  $J = 2.2$  Hz, 1H, C<sub>4</sub>–H), 3.93 (t,  $J = 4.9$  Hz, 1H, C<sub>5</sub>–OH), 3.89 (dd,  $J = 6.0$ , 3.9 Hz, 1H, C<sub>3</sub>–H), 3.71 (qd,  $J = 6.9$ , 6.0 Hz, 1H, C<sub>2</sub>–H), 2.98–2.94 (m, 1H, C<sub>5</sub>–H<sub>a</sub>), 2.70–2.66 (m, 1H, C<sub>5</sub>–H<sub>b</sub>), 2.12–2.02 (br m, 1H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 1.44–1.34 (br m, 1H, C<sub>4</sub>–H), 1.13 (d,  $J = 6.9$  Hz, 3H, C<sub>2</sub>–CH<sub>3</sub>), 0.86 (d,  $J = 6.8$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.83 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.61 (d,  $J = 6.7$  Hz, 3H, C<sub>4</sub>–CH(CH<sub>3</sub>)<sub>2</sub>), 0.49 (d,  $J = 7.0$  Hz, 3H, C<sub>4</sub>–CH<sub>3</sub>), –0.05 (s, 3H, SiCH<sub>3</sub>), –0.10 (s, 3H, SiCH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz, 300 K)  $\delta$  174.7, 152.2, 143.1, 138.2, 128.8, 128.5, 128.3, 127.8, 125.3, 124.8, 88.5, 73.0, 64.6, 62.6, 42.1, 40.1, 29.7, 25.9, 21.3, 18.0, 15.52, 15.44, 12.9, –4.2, –4.4; IR (KBr)  $\nu_{\max}$  3437s, 2961m, 2931m, 1787s, 1690m, 1451m, 1384m, 1362m, 1252m, 1207m, 1178m, 1082m, 1052m, 991m, 838m, 705m cm<sup>-1</sup>; MS (ES+)  $m/z$  (%) 1101 (42, [2 M + Na]<sup>+</sup>), 829 (12, [3 M + Ca]<sup>2+</sup>), 562 (100, [M + Na]<sup>+</sup>), 522 (28, [MH – H<sub>2</sub>O]<sup>+</sup>).

**(3R,4S,5S)-4-(tert-Butyldimethylsilyloxy)-3,5-dimethyl-tetrahydro-pyran-2-one (6a).** To a solution of crude **5a** (39 g) in THF (220 mL) at 0 °C under an atmosphere of argon was added a solution of *t*-BuOK (1 M in THF, 1.2 mL, 1.2 mmol). The resulting reaction mixture was stirred for 30 min at 0 °C, whereas cleaved oxazolidinone precipitated gradually as a colorless solid. THF was removed under reduced pressure, and the residue was taken in heptane (500 mL). After stirring for 30 min at 0 °C, the resulting suspension was filtrated and the residue was washed with heptane (250 mL) (14.5 g of pure oxazolidinone **7** was isolated by this process). The filtrate was collected and concentrated in vacuo to give the crude lactone. Purification by Kugelrohr distillation (200 °C, 0.065 mbar) afforded 13.4 g (88% over three steps) of pure product **6a** as a colorless crystalline solid: mp 53–54 °C;  $R_f = 0.49$  (SiO<sub>2</sub>, 1:1 heptane–AcOEt); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 500 MHz, 300 K)  $\delta$  4.18 (dd,  $J = 10.8$ , 4.6 Hz, 1H, C<sub>6</sub>–H<sub>a</sub>), 4.05 (dd,  $J = 10.8$ , 8.7 Hz, 1H, C<sub>6</sub>–H<sub>b</sub>), 3.82 (dd,  $J = 5.1$ , 2.9 Hz, 1H, C<sub>4</sub>–H), 2.45 (qd,  $J = 7.5$ , 5.1 Hz, 1H, C<sub>3</sub>–H), 2.21 (dqdd,  $J = 8.7$ , 6.9, 4.6, 2.9 Hz, 1H, C<sub>5</sub>–H), 1.19 (d,  $J = 7.5$  Hz, 3H, C<sub>3</sub>–CH<sub>3</sub>), 0.89 (d,  $J = 6.9$  Hz, 3H, C<sub>5</sub>–CH<sub>3</sub>), 0.87 (s, 9H, SiC(CH<sub>3</sub>)<sub>3</sub>), 0.072 (s, 3H, SiCH<sub>3</sub>), 0.067 (s, 3H, SiCH<sub>3</sub>); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 125 MHz, 300 K):  $\delta$  172.9, 72.5, 69.7, 42.7, 30.0, 25.6, 17.7, 15.2, 11.3, –4.79, –4.81; IR (KBr)  $\nu_{\max}$  2958m, 2928m, 2855m, 1727s, 1473m, 1257m, 1207m, 1126m, 1113m, 1049s, 1018m, 996m, 853s, 837s, 778s cm<sup>-1</sup>; MS (ES+)

$m/z$  (%) 539 (30,  $[M + 2 Na]^+$ ), 322 (55,  $[M + CH_3CN]^+$ ), 281 (100,  $[M + Na]^+$ ).

**(2R,3S,4S)-3-(tert-Butyldimethylsilyloxy)-5-hydroxy-2,4-dimethyl-pentanoic Acid Methoxy-methyl-amide (14).**

A solution of **6a** (1.80 g, 6.96 mmol) in THF (23 mL) at 23 °C under an atmosphere of argon was treated with *N,O*-dimethylhydroxylamine hydrochloride (1.05 g, 10.79 mmol), and the resulting suspension was cooled at -15 °C. A solution of isopropylmagnesium chloride in THF (2 M, 10.5 mL, 20.9 mmol) was added dropwise over a period of 40 min (exothermic), whereas the reaction mixture became a clear gray-colored solution which was further stirred between -15 °C and -10 °C for 1 h and 20 min before being worked up by dilution with TBME (20 mL) followed by addition of a 1:1 v/v mixture of saturated aqueous  $NH_4Cl$  and water (40 mL). The mixture was allowed to warm up at 23 °C and was stirred until the salts had dissolved. The layers were separated, and the aqueous layer was extracted with TBME (15 mL). The organic extracts were washed with saturated aqueous NaCl (3 × 25 mL), combined, dried ( $MgSO_4$ ), and concentrated in vacuo to give the crude alcohol **14** (2.18 g, 98%) as colorless crystals which did not require further purification: mp 28.9–29.8 °C;  $R_f = 0.18$  ( $SiO_2$ , 1:1 heptane–AcOEt);  $^1H$  NMR (DMSO, 500 MHz, 300 K)  $\delta$  4.29 (dd,  $J = 5.1, 4.7$  Hz, 1H,  $C_5-OH$ ), 3.87 (dd,  $J = 5.5, 5.2$  Hz, 1H,  $C_3-H$ ), 3.67 (s, 3H,  $N-OCH_3$ ), 3.46 (m, 1H,  $C_5-H_a$ ), 3.16–3.07 (m, 1H,  $C_5-H_b$ , partially obscured by  $N-CH_3$ ), 3.07 (s, 3H,  $N-CH_3$ ), 3.08–2.97 (br m, 1H,  $C_2-H$ , partially obscured by  $N-CH_3$ ), 1.70–1.59 (br m, 1H,  $C_4-H$ ), 0.99 (d,  $J = 6.9$  Hz, 3H,  $C_2-CH_3$ ), 0.89 (d,  $J = 7.0$  Hz, 3H,  $C_4-CH_3$ ), 0.88 (s, 9H,  $SiC(CH_3)_3$ ), 0.04 (s, 3H,  $SiCH_3$ ), -0.01 (s, 3H,  $SiCH_3$ );  $^{13}C$  NMR (DMSO- $d_6$ , 125 MHz, 300 K) 175.3, 74.7, 62.5, 61.1, 41.0, 37.9, 31.8, 26.0, 18.1, 14.1, 13.4, -4.1, -4.2; IR (film)  $\nu_{max}$  3450m, 2956s, 2938s, 2885m, 2857m, 1634m, 1463m, 1386m, 1255s, 1102m, 1073m, 1050m, 1004m, 869m, 837s, 775s  $cm^{-1}$ ; MS (ES+)  $m/z$  (%) 661 (40,  $[2 M + Na]^+$ ), 499 (23,  $[3 M + Ca]^{2+}$ ), 491 (8,  $[3 M + Na + H]^{2+}$ ), 342 (100,  $[M + Na]^+$ ), 320 (57,  $[M + H]^+$ ).

**Crystal Structure Analysis of 8:** Crystals suitable for diffraction experiments grown from  $CH_2Cl_2$ /hexane.  $C_{25}H_{31}NO_5$ ,  $M_r = 425.51$ , orthorhombic, space group  $P2_12_12_1$  (No. 19) with  $a = 8.414(1)$  Å,  $b = 13.760(2)$  Å,  $c = 19.299(2)$

Å,  $V = 2234.4(5)$  Å<sup>3</sup>,  $Z = 4$ ,  $D_c = 1.265$  g·cm<sup>-3</sup>, 61 492 reflections measured, 4070 independent ( $R_{int} = 0.0375$ ),  $3.95^\circ < \theta < 68.24^\circ$ , 404 parameters, 0 restraints,  $R_1 = 0.0244$ ,  $wR_2 = 0.0604$  for 3989 reflections with  $I > 2\sigma(I)$ ,  $R_1 = 0.0251$ ,  $wR_2 = 0.0610$  for all 4070 data, GoF = 1.049, Flack  $x = 0.01(11)$ , res. el. dens. = +0.17/-0.19 e·Å<sup>3</sup>. Diffraction data were collected at 100 K with a Bruker AXS SMART 6000 CCD detector on a three-circle platform goniometer with Cu  $K\alpha$  radiation from a fine-focus sealed tube generator equipped with a graphite monochromator. A semiempirical absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings.<sup>15</sup> The structure was solved and refined on  $F^2$  with the SHELXTL suite of programs.<sup>16</sup> Non-hydrogen atoms were refined with anisotropic displacement parameters; all hydrogen atoms could be located in DF maps and were refined isotropically.

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### Supporting Information Available

Detailed descriptions of experimental procedures for the synthesis of **6a** (according to Scheme 1), **6b**, and **10** with analytical data. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 228658.

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