Organic Process Research & Development

Communication

pubs.acs.org/OPRD

Rapid and Scalable Access into Strained Scaffolds through Continuous Flow Photochemistry

Daniel Blanco-Ania,[†] Sagar Ashok Gawade,[†] Luc J. L. Zwinkels,[†] Luuk Maartense,[†] Marjon G. Bolster,[‡] Jorg C. J. Benningshof,[‡] and Floris P. J. T. Rutjes*[,†]

[†]Institute for Molecules and Materials, Radboud University, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands

[‡]Mercachem B.V., Kerkenbos 1013, 6546 BB Nijmegen, The Netherlands

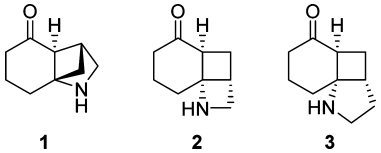
Supporting Information

ABSTRACT: Two conformationally restricted three-dimensional aminoketone scaffolds have been synthesized in only three steps, using a continuous flow photochemistry approach, which is also amenable to scale-up. In addition, several approaches to further derivatize these scaffolds for the synthesis of low molecular weight compound libraries have been detailed.

In order to address the continuous search for new and unique small molecules that can be used in screening campaigns to identify new starting points for drug discovery, the European Lead Factory has been established.[1] In a pan-European consortium of big pharma companies, SMEs, and academic groups, focused compound libraries are being produced based predominantly on rigid, nonplanar scaffolds. Besides creating this unique library of low molecular weight compounds, another major task of the consortium is to acquire and develop high-throughput assays for new biological targets. In a collaborative effort, and in conjunction with previous continuous flow research in our group,[2] we have explored photochemical reactions in microreactors[3] as a possible means to gain rapid access to highly constrained, three-dimensional scaffolds that can serve as a starting point for preparing focused compound libraries.

The [2 + 2] photocycloaddition is a well-established and powerful approach to prepare strained carbocyclic structures,[4] including applications in complex natural products.[5] Inspired by these approaches, we have identified the three nitrogen-containing tricyclic scaffolds **1**−**3** as potential unique starting points for library synthesis (Scheme 1), which we anticipated should be readily accessible from commercially available starting materials. Interestingly, while the corresponding carbacyclic (methylene instead of NH),[6] and oxacyclic (O instead of NH)[7] systems have been prepared before, the synthesis of these nitrogen-containing derivatives through [2 + 2] photocycloaddition has not been reported.[8] We also envisioned that the combination of ketone and nitrogen functional groups in different positions, might serve as versatile handles for further functionalization to create focused compound libraries. In this communication, we will demonstrate that the cycloaddition pathway is a viable approach to these new scaffolds, which is also amenable to scale-up. Furthermore, several pathways for functionalization in order to validate the future synthesis of a full-blown library have been probed.

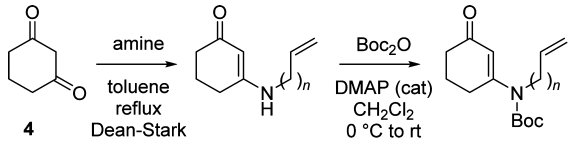
Scheme 1. Target Scaffolds 1−3 for Library Synthesis



1 **2** **3**

The synthesis pathway commenced with the condensation of cyclohexane-1,3-dione (**4**) with two alkenylamines in refluxing toluene using a Dean−Stark apparatus,[9] resulting in the corresponding enaminones **5a**[10] and **5b** in excellent yields

Scheme 2. Precursor Synthesis



4

5a: n = 1
5b: n = 2

6a: n = 1 (65%)
6b: n = 2 (60%)

(Scheme 2). The crude products appeared sufficiently pure by ^{1}H NMR and were therefore without further purification subjected to Boc-protection under standard conditions (Boc_2O, DMAP (10 mol %), CH_2Cl_2) to form the photochemical precursors **6a** and **6b** in 65 and 60% yield (over two steps), respectively, after purification by silica gel chromatography.

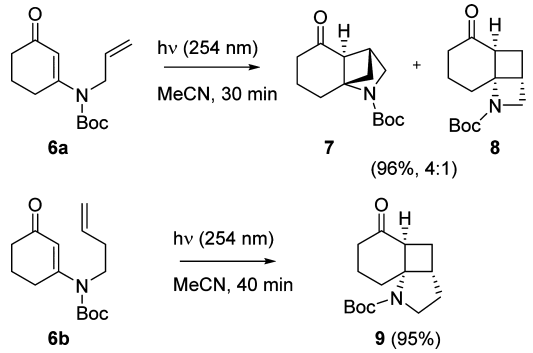
With these precursors in hand, we set out to explore the photocycloadditions in a continuous flow system (Scheme 3) because of shorter reaction times and higher yields than batch photochemical reactions.[11] Initial explorative small scale reactions and subsequent optimization were carried out in a self-made flow system: an HPLC pump was used to pump the liquid phase through fluorinated ethylene propylene (FEP) tubing (inner diameter 1.6 mm, internal volume 11.6 mL), which was wound around a condenser. This unit was irradiated

Special Issue: Continuous Processing, Microreactors and Flow Chemistry

Received: October 31, 2015

DOI: 10.1021/acs.oprd.5b00354
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 3. [2 + 2] Photocycloaddition Reactions



in a Rayonet RMR-600 photochemical reactor, using lamps of different wavelengths (Figure 1). The first reactions were

Figure 1. Small scale photochemical flow reactor.

carried out using allyl-substituted amine **6a**, using irradiation with both 300 and 254 nm and by applying different solvents. The conversion was most conveniently monitored by TLC, residence times were adjusted by changing the flow rate such that full conversion was reached. In all solvents that were evaluated (MeCN, acetone, diethyl ether, *n*-hexanes, THF), mixtures of the "crossed" product **7** and the "straight" product **8** were obtained.[12] Since we did not observe a significant difference in outcome between irradiation by 300 or 254 nm (neither in yield nor in ratio), we chose to conduct all experiments at 254 nm since this was the only wavelength we could apply during scale-up in a larger system. Ratios of products **7** and **8** ranged from approximately 2.5:1 for the less polar solvents (*n*-hexanes, cyclohexane) to 3.5:1 for the more polar solvents (diethyl ether, acetone). The temperature is somewhat difficult to determine: while the cooling water keeps the inner part of the flow system at approximately 4 °C, the temperature at the outside of the tubing is 32 °C due to the heat that is generated by the lamps. We noticed, however, that there is no major influence of the temperature on the outcome of the reaction. The optimal result was eventually obtained using a 40 mM solution of **6a** in MeCN as the solvent, 254 nm irradiation with a 30 min residence time, producing a 4:1 mixture of products **7** and **8** in 96% yield after silica gel purification. Both products behave very similar on the column, so that only the major product **7** could be obtained in pure form, while compound **8** even after extensive chromatography was always obtained as a mixture.[13,14]

Application of identical conditions to the homologous precursor **6b** worked equally well, albeit that a slightly longer residence time of 40 min was required to reach full conversion to the "straight" photocycloadduct **9**.[15] Again, an excellent yield is obtained after chromatography (95%); however, the product appeared not fully stable. Upon standing at room temperature, the quality of the product slowly deteriorates over a period of hours.

Using the Rayonet photoreactor, we were able to reach a throughput of approximately 5.6 g/day, which is insufficient if such a scaffold is to be used as the core building block of a large compound library. Therefore, inspired by a publication of the Booker-Milburn group,[16] we fabricated a higher throughput system, built around a larger commercially available lamp (Figure 2). This system consists of a Philips PL-L 55W UV−C (254 nm) lamp and FEP tubing (id 2.7 mm, reactor volume 105 mL), which is wound around the lamp. The tubing is externally cooled with water and contained in a metal jacket to protect the surrounding from the UV-light. This system reaches a significantly higher throughput and is capable of producing >100 g of product per day. By using the larger scale flow photoreactor, we have been able to convert "pilot" batches varying between 10 and 20 g of both **6a** (total running time: 4.75 and 9.5 h) and **6b** (total running time: 7.3 and 14.6 h) into the corresponding products in similar high isolated yields.

Having thus access to larger amounts of the scaffold molecules, we had to validate chemical reactions that allow the further functionalization of these scaffolds (Scheme 4). Initially, validation chemistry was carried out on scaffold **7** involving for example reductive amination with pyrrolidine (pyrrolidine, AcOH, $NaBH(OAc)_3$, ethylene dichloride) as a representative secondary amine to give compound **10** as a single diastereoisomer in 37% yield. The relative stereochemistry was proven by 2D-NMR, indicating that hydride attack took place from the least hindered rear side of the

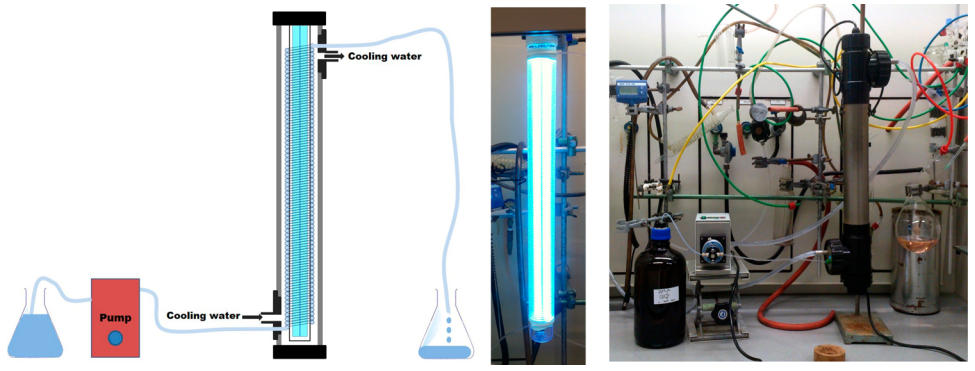
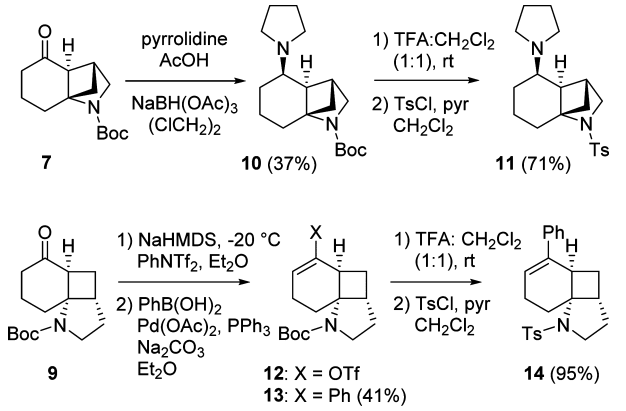


Figure 2. Large scale photochemical flow reactor: schematic overview and complete setup.

DOI: 10.1021/acs.oprd.5b00354
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 4. Functionalization Reactions of Scaffolds 7 and 9



intermediate iminium ion. Subsequent Boc-deprotection (TFA:CH_2Cl_2 1:1, 20 min, rt), followed by reaction with tosyl chloride delivered sulfonamide **11** in 71% yield over two steps after purification.

On the other hand, cycloadduct **9** was used to probe Suzuki cross-coupling on the ketone functional group. Thus, enolization at −20 °C using NaHMDS in Et_2O, followed by quenching with $PhNTf_2$ produced the corresponding vinyl triflate **12**. Subjection of the crude product to Suzuki conditions $PhB(OH)_2$, $Pd(OAc)_2/PPh_3$, aqueous sodium carbonate in dioxane, rt) yielded the desired cross-coupled product **13** in 41% yield over two steps after silica gel purification. Further functionalization as of compound **10** (Boc-deprotection and subsequent sulfonamide formation) produced sulfonamide **14** in 95% yield over two steps after purification

In summary, we have shown that two conformationally restricted three-dimensional aminoketone scaffolds can be rapidly built-up in only three steps, using a continuous flow photochemistry approach. We also showed that this pathway can be conveniently scaled up, using identical conditions simply in a larger photoreactor. Finally, several approaches to further functionalize these scaffolds have been detailed. The synthesis of a 400-membered compound library, using these scaffolds and the functionalization pathway is currently underway in our laboratories.

EXPERIMENTAL SECTION

***tert*-Butyl allyl(3-oxocyclohex-1-en-1-yl)carbamate (6a).** A solution of cyclohexane-1,3-dione (**4**, 10.0 g, 89.2 mmol) and allylamine (7.64 g, 134 mmol) in toluene (180 mL) was refluxed using a Dean−Stark setup. The reaction was monitored by TLC, and upon completion (5 h) the mixture was evaporated under reduced pressure to give enaminone **5a** (13.8 g, 88.3 mmol, 99%) as a colorless oil.[10] The crude product was subjected to Boc-protection without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, J = 17.1, 10.2, 5.7 Hz, 1H), 5.27−5.17 (m, 2H), 5.11 (s, 1H), 4.87 (s, 1H), 3.70 (tt, J = 5.5, 1.4 Hz, 2H), 2.35 (t, J = 6.2 Hz, 2H), 2.32−2.28 (m, 2H), 2.00−1.92 (m, 2H). A solution of enaminone **5a** (1.00 g, 6.61 mmol) in CH_2Cl_2 (10 mL) was treated with Boc_2O (2.10 g, 9.92 mmol) and 4-(dimethylamino)pyridine (81 mg, 0.66 mmol) at 0 °C. After stirring for 5 min, the ice bath was removed, and stirring was continued for 5 h at room temperature. The reaction mixture was diluted with water (20 mL), extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (1 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo. After purification with flash column chromatography (EtOAc/heptane 1:7 → 2:3), carbamate **6a** (992 mg, 3.95 mmol, 65%) was obtained as a colorless oil. IR (ATR) ν 2976, 1712, 1658, 1588, 1367, 1134 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.2, 10.4, 4.9 Hz, 1H), 5.72 (t, J = 1.8 Hz, 1H), 5.18 (dtd, J = 10.4, 1.7, 1.1 Hz, 1H), 5.13 (dtd, J = 17.2, 1.8, 1.1 Hz, 1H),, 4.19 (dt, J = 4.9, 1.8 Hz, 2H), 2.79−2.73 (m, 2H), 2.38 (dd, J = 7.2, 6.0 Hz, 2H), 2.03−1.95 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.65, 163.40, 152.43, 132.71, 116.47, 114.95, 82.52, 51.89, 36.89, 30.45, 28.09, 23.33; HRMS (ESI$^+$) calcd for $(C_{14}H_{21}NO_3 + Na)^+$ 274.1419, found 274.1415..

***tert*-Butyl but-3-en-1-yl(3-oxocyclohex-1-en-1-yl)-carbamate (6b).** A solution of cyclohexane-1,3-dione (10.0 g, 89.2 mmol) and but-3-enylamine (9.51 g, 134 mmol) in toluene (180 mL) was refluxed using a Dean−Stark apparatus. The reaction was monitored by TLC, and upon completion (5 h) the mixture was evaporated under reduced pressure to give enaminone **5b** (14.6 g, 88.3 mmol, 99%) as a colorless oil. The crude mixture was subjected to Boc-protection without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85−5.70 (m, 1H), 5.19−5.11 (m, 2H), 5.14 (s, 1H), 4.61 (br s, 1H), 3.16 (td, J = 6.8, 5.3 Hz, 2H), 2.43−2.29 (m, 6H), 2.04−1.92 (m, 2H). A solution of enaminone **5b** (1.55 g, 0.41 mmol) in CH_2Cl_2 (30 mL) was treated with Boc_2O (3.08 g, 14.1 mmol) and 4-(dimethylamino)pyridine (115 mg, 0.94 mmol) at 0 °C. After stirring for 15 min, the ice bath was removed, and stirring was continued for 6 h at room temperature. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL); the combined organic layers were washed with brine (1 × 30 mL), dried ($MgSO_4$), and concentrated in vacuo. After purification with flash column chromatography (15 → 25% EtOAc/heptane), carbamate **6b** (1.47 g, 5.55 mmol, 60% over two steps) was obtained as a colorless oil. IR (ATR) ν 2977, 1709, 1656, 1587, 1367 cm^{-1}; 5.72 (ddt, J = 17.1, 10.2, 7.0 Hz, 1 H), 5.70 (s, 1H), 5.10−5.00 (m, 2H), 3.67−3.57 (m, 2H), 2.73−2.65 (m, 2 H), 2.40−2.27 (m, 4H), 2.01−1.92 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.73, 163.27, 152.70, 134.49, 117.41, 115.49, 82.44, 48.46, 36.99, 32.83, 30.81, 28.24, 23.41; HRMS (ESI$^+$) calcd for $(C_{15}H_{23}NO_3 + Na)^+$ 288.1576, found 288.1578.

Photochemical Cycloaddition of Compound 6a. A solution of enaminone **6a** (4.87 g, 19.4 mmol) in acetonitrile (485 mL, 40 mM) was pumped through FEP tubing (id: 2.7 mm, total volume 140 mL, irradiated volume 105 mL) at a flow of 3.5 mL/min, corresponding to a 36.7 min irradiation time using 254 nm UV light. After concentrating the reaction mixture in vacuo, a 4:1 mixture of compounds **7** and **8** (4.69 g, 18.7 mmol, 96% combined yield) was obtained after a first purification by column chromatography (EtOAc/heptane 1:7 → 1:4). A second purification over silica gel yielded **7** in pure form, along with a mixture of the two cycloadducts.

***tert*-Butyl (*rel*-3*R*,3a*S*,7a*S*)-4-oxohexahydro-3,7a-methanoindole-1(2*H*)-carboxylate (7).** IR (ATR) ν 2975, 1692, 1364, 1121 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (d, J = 8.8 Hz, 1H), 3.27 (d, J = 8.8 Hz, 1H), 2.98 (tt, J = 2.8, 1.2 Hz, 1H), 2.93 (d, J = 11.9 Hz, 1H), 2.51−2.47 (m, 1H), 2.28−2.15 (m, 3H), 2.11−2.04 (m, 1H), 1.98−1.89 (m, 2H), 1.55 (dd, J = 7.3, 1.3 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.82, 156.43, 79.47, 77.43, 58.86, 47.90, 43.50, 39.97, 38.24, 28.33, 28.15, 25.36; HRMS (ESI$^+$) calcd for $(C_{14}H_{21}NO_3 + Na)^+$ 274.1419, found 274.1417.

DOI: 10.1021/acs.oprd.5b00354
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

***tert*-Butyl (*rel*-1*S*,4*R*,6*S*)-7-oxo-2-azatricyclo[4.4.0.0^{1,4}]-decane-2-carboxylate (8, Analytical Sample Obtained in Pure Form).** IR (ATR) ν 2929, 1689, 1364, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (dd, J = 8.9, 1.1 Hz, 1H), 3.37 (dt, J = 8.8, 1.1 Hz, 1H), 3.12 (dt, J = 3.1, 1.0 Hz, 1H), 2.48 (d, J = 14.8 Hz, 1H), 2.42−2.33 (m, 2H), 2.32−2.09 (m, 4H), 1.94 (ddd, J = 8.0, 3.0, 0.7 Hz, 1H), 1.68 (dt, J = 13.4, 3.9 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.86, 155.65, 79.62, 75.32, 61.30, 51.88, 40.73, 38.86, 37.24, 28.58, 27.08, 23.67; HRMS (ESI$^+$) calcd for $(C_{14}H_{21}NO_3 + Na)^+$ 274.1419, found 274.1416.

***tert*-Butyl (*rel*-3a*R*,4a*S*,8a*S*)-5-oxooctahydrobenzo-[1,4]cyclobuta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (9).** A solution of enaminone **6b** (4.16 g, 15.7 mmol) in acetonitrile (530 mL, 30 mM) was pumped through FEP tubing at a flow rate of 2.88 mL/min, corresponding to a 40 min irradiation time using 254 nm UV light. After concentrating the reaction mixture in vacuo, cycloadduct **9** (3.95 g, 14.9 mmol, 95%) was obtained as a colorless oil. Upon standing, even at low temperatures, the compound slowly decomposes. Therefore, follow-up reactions were carried out immediately after the photocycloaddition. IR (ATR) ν 2947, 1686, 1364, 1161, 1115 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, −50 °C, mixture of rotamers) δ 3.69−3.46 (m, 2H), 2.88−2.67 (m, 2H), 2.56−2.32 (m, 2H), 2.27−2.12 (m, 2H), 2.08−1.91 (m, 2H), 1.90−1.74 (m, 1H), 1.73−1.51 (m, 2H), 1.41−1.37 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$, −50 °C) δ (major rotamer) 214.92, 154.16, 80.11, 68.94, 48.65, 47.39, 41.16, 40.39, 29.82, 28.50, 26.99, 25.72, 21.45; δ (minor rotamer) 215.61, 154.07, 79.61, 70.48, 47.61, 47.32, 40.82, 40.22, 28.75, 28.42, 26.61, 25.63, 22.00; HRMS (ESI$^+$) calcd for $(C_{15}H_{23}NO_3 + Na)^+$ 288.1576, found 288.1579.

(*rel*-3*R*,3a*R*,4*R*,7a*S*)-*tert*-Butyl 4-(pyrrolidin-1-yl)-hexahydro-3,7a-methanoindole-1(2*H*)-carboxylate (10). Acetic acid (24 mg, 0.40 mmol), pyrrolidine (28 mg, 0.40 mmol), $NaBH(OAc)_3$ (152 mg, 0.72 mmol), and molecular sieves (4 Å) were added to a solution of ketone **7** (100 mg, 0.40 mmol) in 1,2-dichloroethane (2 mL). The mixture was stirred at room temperature for 48 h (additional pyrrolidine (28 mg, 0.40 mmol) was added after 24 h). The reaction was quenched with water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL); the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), and concentrated in vacuo. After purification by column chromatography (EtOAc/heptane 4:1 → 1:0) compound **10** (45 mg, 0.15 mmol, 37%) was obtained as a colorless oil. IR (ATR) ν 1689, 1365, 1123 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.32 (d, J = 8.6 Hz, 1H), 3.28 (d, J = 8.6 Hz, 1H), 3.11 (dd, J = 6.7, 2.5 Hz, 1H), 2.83−2.78 (m, 1H), 2.72−2.38 (m, 5H), 2.26−2.17 (m, 1H), 2.11−1.96 (m, 1H), 1.88 (d, J = 14.1 Hz, 1H), 1.78 (dd, J = 8.0, 6.6 Hz, 1H), 1.76−1.65 (m, 4H), 1.65−1.54 (m, 1H), 1.49−1.42 (m, 1H), 1.45 (s, 9H), 1.26−1.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.26, 78.94, 72.16, 61.41, 56.01, 53.70, 53.59, 38.96, 38.73, 29.13, 28.78, 28.58, 23.84, 17.62; HRMS (ESI$^+$) calcd for $(C_{18}H_{30}N_2O_2 + H)^+$ 307.2386, found 307.2389.

(*rel*-3*R*,3a*R*,4*R*,7a*S*)-4-(Pyrrolidin-1-yl)-1-tosyloctahydro-3,7a-methanoindole (11). A solution of pyrrolidine **10** (17 mg, 0.055 mmol) was stirred at room temperature in a TFA/CH_2Cl_2 mixture (1:1) for 20 min. The mixture was concentrated, dissolved in CH_2Cl_2 (1 mL), and at 0 °C treated with triethylamine (17 mg, 0.17 mmol) and *p*-toluenesulfonyl chloride (11 mg, 0.055 mmol). After stirring for 2.5 h at room temperature, the reaction was quenched with water (1.5 mL) and extracted with CH_2Cl_2 (3 × 3 mL); the combined organic layers were washed with brine (4 mL), dried ($MgSO_4$) and concentrated in vacuo. After purification by column chromatography sulfonamide **11** (14 mg, 0.039 mmol, 71% over two steps) was obtained as a colorless oil. IR (ATR) ν 2925, 1702, 1322, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.63 (m, 2H), 7.36−7.24 (m, 2H), 3.44 (d, J = 8.4 Hz, 1H), 3.30 (d, J = 8.3 Hz, 1H), 2.90 (d, J = 5.0 Hz, 1H), 2.74 (s, 1H), 2.61−2.34 (m, 8H), 2.40 (s, 3H), 2.11−2.00 (m, 2H), 1.86 (d, J = 14.0 Hz, 1H), 1.74 (t, J = 6.8 Hz, 1H), 1.72−1.43 (m, 6H), 1.22 (t, J = 12.8 Hz, 1H), 0.60 (t, J = 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.20, 136.26, 129.73, 128.27, 74.66, 60.94, 55.62, 54.70, 53.54, 38.97, 35.26, 28.97, 27.94, 23.79, 21.65, 17.22; HRMS (ESI$^+$) calcd for $(C_{20}H_{28}N_2O_2S + H)^+$ 361.1950, found 361.1954.

***tert*-Butyl (*rel*-3a*R*,4a*R*,8a*S*)-5-Phenyl-3,3a,4,4a,7,8-hexahydrobenzo[1,4]cyclobuta[1,2-*b*]pyrrole-1(2*H*)-carboxylate (13).** NaHMDS (643 μL of a 2 M solution in THF, 1.286 mmol) was added to a solution of compound **9** (310 mg, 1.168 mmol) in Et_2O (3 mL) at −20 °C, and after 20 min $PhNTf_2$ (417 mg, 1.168 mmol). After warming to room temperature, the mixture was stirred for 4 h. Then, the temperature was lowered to −20 °C and NaHMDS (117 μL of a 2 M solution in THF, 0.117 mmol) was added and after 20 min $PhNTf_2$ (42 mg, 0.117 mmol). After 4 h, the same additions were performed. The reaction mixture was stirred for 10 h at room temperature and then washed with saturated aqueous $NaHCO_3$ (2 × 4 mL) and water (4 mL). The combined aqueous phase was reextracted with Et_2O (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to obtain vinyl triflate **12** (slightly contaminated with PhNHTf). The crude mixture was used for the Suzuki coupling reaction. A mixture of vinyl triflate **12**, $Pd(OAc)_2$ (38 mg, 0.17 mmol), PPh_3 (133 mg, 0.507 mmol), and 1.0 M aqueous sodium carbonate (2.34 mL) were dissolved in 1,4-dioxane (6.5 mL). The mixture was stirred for 30 min at room temperature. Then, phenylboronic acid (171 mg, 1.402 mmol) was added, and the mixture was stirred for 20 h. The reaction was quenched with water (4 mL) and extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with brine (8 mL), dried ($MgSO_4$), concentrated in vacuo, and purified via silica column chromatography (EtOAc/heptane 0 → 7%) to yield compound **13** (156 mg, 0.480 mmol, 41% over two steps) as a white solid. IR (ATR) ν 2977, 2928, 1688, 1363, 1170, 764, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H), 6.1 (d, J = 5.9 Hz, 1H), 3.85−3.63 (m, 2H), 3.20−3.02 (m, 1H), 2.82−2.76 (m, 1H), 2.52−2.42 (m, 1H), 2.38−2.11 (m, 3H), 2.01−1.87 (m, 1H), 1.82 (ddd, J = 12.2, 9.1, 3.4 Hz, 1H), 1.78−1.63 (m, 1H), 1.40 (s, 9H), 1.40−1.33 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.89. 140.70, 140.67. 128.34, 126.78, 125.31, 122.55, 79.35, 67.14, 47.85, 38.88, 38.28, 31.79, 28.67, 27.35, 25.59, 24.69; HRMS (ESI$^+$) calcd for $(C_{21}H_{27}NO_2 + Na)^+$ 348.1940, found 348.1942.

(*rel*-3a*R*,4a*R*,8a*S*)-5-Phenyl-1-tosyl-1,2,3,3a,4,4a,7,8-octahydrobenzo[1,4]cyclobuta[1,2-*b*]pyrrole (14). A solution of Suzuki product **13** (27 mg, 0.083 mmol) was stirred at room temperature in a TFA/CH_2Cl_2 mixture (1:1, 2 mL) for 15 min. The mixture was concentrated, dissolved in CH_2Cl_2 (1 mL), and at 0 °C treated with triethylamine (21 mg, 0.207 mmol) and *p*-toluenesulfonyl chloride (16 mg, 0.084 mmol). After stirring for 2.5 h at room temperature, the reaction was quenched with a saturated solution of $NaHCO_3$ (1 mL), extracted with CH_2Cl_2 (3 × 2 mL), the combined organic

DOI: 10.1021/acs.oprd.5b00354
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

layers were washed with brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo. After purification by column chromatography (EtOAc/heptane (1:5) sulfonamide **14** (29 mg, 0.079 mmol, 95% over two steps) was obtained as a white solid. IR (ATR) ν 2924, 1598, 1157, 763, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.64 (m, 2H), 7.28−7.23 (m, 2H), 7.22−7.18 (m, 1H), 7.16−7.12 (m, 2H), 7.11−7.07 (m, 2H), 6.26−6.21 (m, 1H), 3.75 (ddd, J = 9.3, 8.0, 1.2 Hz, 1H), 3.65 (ddd, J = 10.9, 9.7, 6.2 Hz, 1H), 2.92 (dd, J = 9.5, 4.6 Hz, 1H), 2.90−2.83 (m, 1H), 2.57−2.43 (m, 2H), 2.34−2.25 (m, 1H), 2.27 (s, 3H), 2.06 (ddd, J = 12.1, 9.5, 6.8 Hz, 1H), 1.91 (dddd, J = 12.8, 11.0, 8.0, 7.3 Hz 1H), 1.73 (ddd, J = 12.2, 9.4, 4.7 Hz, 1H), 1.67 (dd, J = 12.8, 6.1 Hz, 1H), 1.60−1.53 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.95, 140.93, 140.33, 137.56, 129.43, 128.10, 127.13, 126.71, 125.12, 123.16, 70.84, 49.07, 40.50, 37.11, 31.67, 27.85, 27.13, 24.51, 21.37; HRMS (ESI^+) calcd for $(C_{23}H_{25}NO_2S + H)^+$ 380.1684, found 380.1694 and calcd for $(C_{23}H_{25}NO_2S + Na)^+$ 402.1504, found 402.1516.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00354.

Spectral data (^1H and ^{13}C NMR of all new compounds) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: F.Rutjes@science.ru.nl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Acknowledgement is made to the Innovative Medicines Initiative Grant (115489, FP7/2007-2013). Jürgen Mateman is kindly acknowledged for initial experiments on the Suzuki coupling reactions.

■ REFERENCES

(1) https://www.europeanleadfactory.eu/ (last accessed at Dec 18, 2015).

(2) See e.g.: (a) Nieuwland, P. J.; Segers, R.; Koch, K.; van Hest, J. C. M.; Rutjes, F. P. J. T. *Org. Process Res. Dev.* **2011**, *15*, 783−787. (b) van den Broek, S. A. M. W.; Leliveld, J. R.; Becker, R.; Delville, M. M. E.; Nieuwland, P. J.; Koch, K.; Rutjes, F. P. J. T. *Org. Process Res. Dev.* **2012**, *16*, 934−938. (c) van den Broek, S. A. M. W.; Becker, R.; Kossl, F.; Delville, M. M. E.; Nieuwland, P. J.; Koch, K.; Rutjes, F. P. J. T. *ChemSusChem* **2012**, *5*, 289−292. (d) Nieuwland, P. J.; Koch, K.; van Harskamp, N.; Wehrens, R.; van Hest, J. C. M.; Rutjes, F. P. J. T. *Chem. - Asian J.* **2010**, *5*, 799−805.

(3) For reviews on photochemical reactions in flow, see: (a) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. - Eur. J.* **2014**, *20*, 10562−10589. (b) Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025−2052. (c) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522−7550.

(4) For selected examples, see, e.g: (a) Buu Hue, B. T.; Dijkink, J.; Kuiper, S.; van Schaik, S.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2006**, *2006*, 127−137. (b) Blaauw, R. H.; Briere, J. F.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Rutjes, F. P. J. T.; Fraanje, J.; Goubitz, K.; Schenk, H.; Hiemstra, H. *Chem. Commun.* **2000**, 1463−1464. (c) Blaauw, R. H.; Brière, J.-F.; de Jong, R.; Benningshof, J. C. J.; van Ginkel, A. E.; Fraanje, J.; Goubitz, K.; Schenk, H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Org. Chem.* **2001**, *66*, 233−242.

(5) For an overview of photochemical reactions in natural product synthesis, see: Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000−1045.

(6) (a) Matlin, A. R.; McGarvey, D. J. *Tetrahedron Lett.* **1987**, *28*, 5087−5090. (b) Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 1292−1299. (c) Becker, D.; Nagler, M.; Hirsh, S.; Ramun, J. *J. Chem. Soc., Chem. Commun.* **1983**, 371−373.

(7) (a) Matlin, A. R.; Turk, B. E.; McGarvey, D. J.; Manevich, A. A. *J. Org. Chem.* **1992**, *57*, 4632−4638. (b) Mattay, J.; Banning, A.; Bischof, E. W.; Heidbreder, A.; Runsink, J. *Chem. Ber.* **1992**, *125*, 2119−2128.

(8) For related thermal [2 + 2] cycloadditions of allenes, see: Lutteke, G.; AlHussainy, R.; Wrigstedt, P. J.; Buu Hue, B. T.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2008**, *2008*, 925−933.

(9) Wang, G.-W.; Miao, C.-B. *Green Chem.* **2006**, *8*, 1080−1085.

(10) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1981**, 114−115.

(11) Matlin, A. R.; Turk, B. E.; McGarvey, D. J.; Manevich, A. A. *J. Org. Chem.* **1992**, *57*, 4632−4638.

(12) For "crossed" and "straight" mixtures of products from similar substrates, see: Swindell, C. S.; Patel, B. P.; deSolms, S. J. *J. Org. Chem.* **1987**, *52*, 2346−2355.

(13) A sample for analytical purposes, however, was obtained in pure form.

(14) Compounds **7** and **8** partially fragmented upon treatment with TFA/CH_2Cl_2 for Boc group removal. This result refrained us from trying to separate the mixture of the unprotected compounds.

(15) Ikeda, M.; Ohno, K.; Homma, K.-I.; Ishibashi, H.; Tamura, Y. *Chem. Pharm. Bull.* **1981**, *29*, 2062−2068.

(16) (a) Maskill, K. G.; Knowles, J. P.; Elliott, L. D.; Alder, R. W.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2013**, *52*, 1499−1502. (b) For other method to scale up photochemical reactions, see: Su, Y.; Kuijpers, K.; Hessel, V.; Noël, T. *React. Chem. Eng.* **2016**, DOI: 10.1039/C5RE00021A.

DOI: 10.1021/acs.oprd.5b00354
Org. Process Res. Dev. XXXX, XXX, XXX−XXX