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COMMUNICATION

A rapid and convergent synthesis of the integrastatin core†

Pamela M. Tadross, Pradeep Bugga and Brian M. Stoltz*

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The tetracyclic core of the integrastatin natural products has been prepared in a convergent and rapid manner. Our strategy relies upon a palladium(II)-catalyzed oxidative cyclization to form the central [3.3.1]-dioxabicycle of the natural product core. Overall, the core has been completed in only 4 linear steps from known compounds.

Since its discovery in 1981, the United Nations and World Health Organization have estimated that HIV/AIDS has claimed more than 25 million lives, placing it among the most destructive pandemics in history.[1] The urgency of the matter is emphasized by the explosion of research over the past 30 years geared toward the development of new therapies aimed at disabling viral replicative processes. One target that holds particular promise for inhibiting viral replication is the enzyme HIV integrase.[2] Because of the potential that integrase inhibitors hold for the advancement of HIV therapy, these compounds are attractive targets for total synthesis and medicinal chemistry.

In particular, the naturally occurring integrastatins A (**1**) and B (**2**) display inhibitory activity against HIV-1 integrase at micromolar concentrations and have thus been attractive targets for therapeutic development (Fig. 1). The integrastatins were initially isolated as racemic compounds in 2002 from an unidentified fungus found in herbivore dung in New Mexico.[3] Both compounds displayed potent inhibition of the strand transfer reaction of recombinant HIV-1 integrase at micromolar concentrations. IC_{50} values for integrastatins A and B are 1.1 μM and 2.5 μM, respectively. Although there have been no reports of the total synthesis of these natural products, two groups have reported syntheses of the tetracyclic core of the integrastatins.[4]

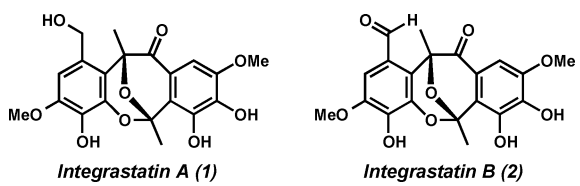

Fig. 1 Integrastatins A (**1**) and B (**2**).

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, California Institute of Technology, Division of Chemistry and Chemical Engineering, Mail Code 101-20, Pasadena, CA, 91125, USA. E-mail: stoltz@caltech.edu; Fax: +1-626-395-8436; Tel: +1-626-395-6064

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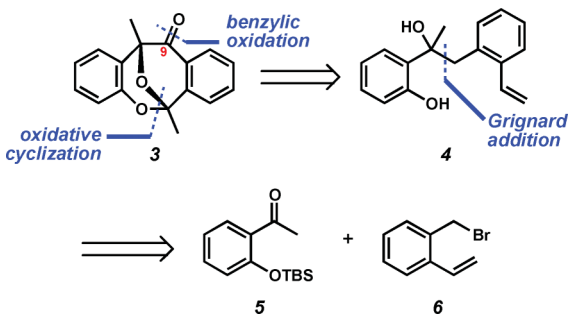
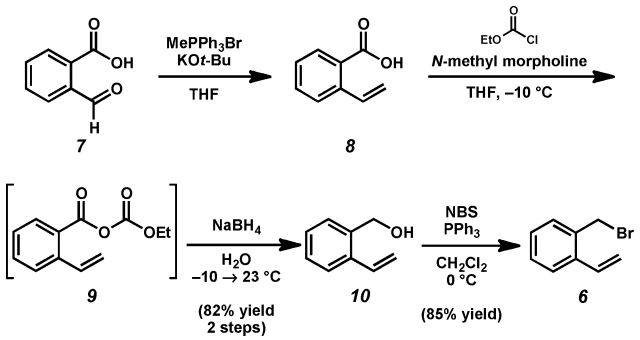
As part of our research program aimed at the total synthesis of natural products by oxidative catalysis,[5] we have targeted the polycyclic [3.3.1]-dioxabicyclic core of the integrastatin natural products. To achieve this, we retrosynthetically disconnected the central [3.3.1]-dioxabicycle (**3**) along the two C–O bonds of the acetal and removed the oxidation at C(9), leading back to diol **4** (Scheme 1). Diol **4** could be prepared in turn from two aromatic fragments (**5** and **6**) of similar complexity by a Grignard addition.



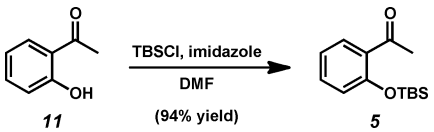
Scheme 1 Retrosynthetic analysis of tetracycle **3**.

In the forward sense, we began with the synthesis of benzylic bromide **6** from commercially available 2-carboxybenzaldehyde (**7**) (Scheme 2). Wittig olefination of benzaldehyde **7** produced styrene **8**,[6] which was subsequently reduced to the primary benzylic alcohol (**10**) through an intermediate mixed anhydride (**9**).[7,8] Moving forward, a number of conditions were examined for the conversion of primary alcohol **10** to the benzylic bromide (**6**); ultimately we found that use of NBS with triphenylphosphine accomplished the transformation in high yield. With benzylic bromide **6** in hand, ketone **5** was prepared in one step from



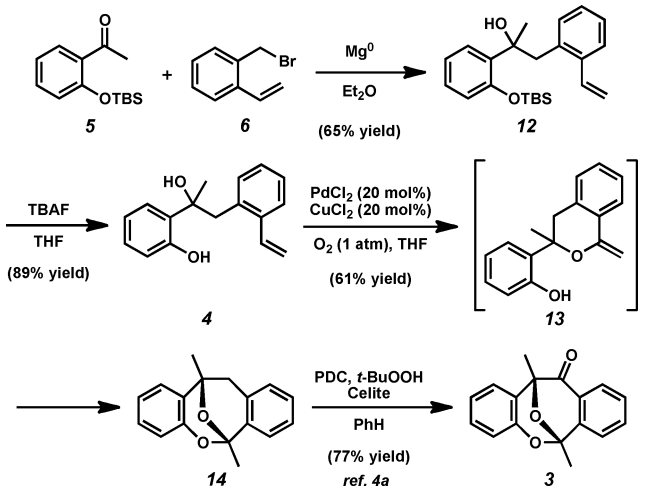
Scheme 2 Preparation of benzylic bromide **6**.

commercially available 2-hydroxyacetophenone (**11**) by protection of the phenol as a silyl ether (Scheme 3).[9]



Scheme 3 Preparation of ketone **5**.

We next turned our attention toward coupling of benzylic bromide **6** and ketone **5** and construction of an appropriate Wacker cyclization substrate. To this end, Grignard addition of the organomagnesium reagent derived from benzylic bromide **6** into ketone **5** furnished tertiary alcohol **12**, which was subsequently desilylated under standard conditions to yield diol **4** (Scheme 4). Treatment of diol **4** with catalytic quantities of $PdCl_2$ and $CuCl_2$ under an oxygen atmosphere resulted in cyclization of both the phenol and tertiary alcohol of diol **4** onto the styrenyl olefin to generate the [3.3.1]-dioxabicycle central to the integrastatin core (**14**).[10] This key cyclization reaction likely proceeds first through palladium-catalyzed formation of a 6-membered ring enol ether (**13**). At this point, the pendant phenol can cyclize onto the enol ether, furnishing the acetal moiety. Importantly, Taylor and co-workers have shown that tetracycle **14** can undergo benzylic oxidation when treated with PDC, Celite, and *t*-BuOOH to produce benzylic ketone **3** in good yield.[4a]



Scheme 4 Coupling of benzylic bromide **6** and ketone **5**, and completion of the integrastatin core.

In summary, we have prepared the tetracyclic core (**14**) of the integrastatin natural products (**1** and **2**) in 30% overall yield and in only 4 linear steps from known compounds. The central [3.3.1]-dioxabicycle was directly generated by a palladium-catalyzed oxidative cyclization of diol **4** to complete the tetracycle synthesis. Efforts are currently underway to apply this transformation to a rapid synthesis of integrastatins A and B and analogs thereof.

Experimental

Materials and methods

Unless stated otherwise, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially obtained reagents were used as received. Styrene **8** was prepared according to the method of Seijas, *et al.*[6] Benzylic alcohol **10** was prepared according to the method of Bonnaud, *et al.*[7] Ketone **5** was prepared according to the method of Murata, *et al.*[9] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, potassium permanganate, or CAM staining. Silia*Flash* P60 Academic Silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ (ppm)) (multiplicity, coupling constant (Hz), integration). Data for ^{13}C spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired either using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode or from the Caltech Mass Spectral Facility.

Benzylic bromide 6

A solution of benzylic alcohol **10** (736 mg, 5.49 mmol) in CH_2Cl_2 (27 mL) was cooled to 0 °C in an ice bath. Triphenylphosphine (1.67 g, 6.36 mmol) was added as a solid in one portion and the resulting solution was maintained at 0 °C for 10 min with stirring. Following this period, *N*-bromosuccinimide (1.13 g, 6.36 mmol) was added portion-wise as a solid over 5 min. The reaction was then maintained with stirring at 0 °C for 20 min or until benzylic alcohol **10** was consumed by TLC analysis. The reaction was concentrated under vacuum and purified by flash chromatography (10 : 1 hexanes : ethyl acetate eluent) to yield benzylic bromide **6** (932 mg, 85% yield): R_f 0.56 (10 : 1 hexanes : ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.51 (m, 1H), 7.35–7.29 (m, 2H), 7.28–7.23 (m, 1H), 7.11 (dd, J = 17.3, 11.0 Hz, 1H), 5.76 (dd, J = 17.3, 1.2 Hz, 1H), 5.45 (dd, J = 11.0, 1.2 Hz, 1H), 4.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.25, 134.56, 133.36, 130.23, 129.13, 128.11, 126.43, 117.08, 31.63; IR (NaCl/film) 3066, 1847, 1627, 1569, 1486, 1453, 1416, 1223, 1210, 1184, 987, 917, 772, 758 cm^{-1}; HRMS (EI+) m/z calc'd for $C_9H_9{}^{79}Br$ $[M]^+$: 195.9888, found 195.9897.

Tertiary alcohol 12

A flame-dried reaction flask was charged with Mg turnings (141 mg, 5.79 mmol). The flask was evacuated and backfilled with nitrogen. Diethyl ether (5 mL) was added, followed by 1,2-dibromoethane (20 μL). The suspension was stirred for 15 min and then concentrated under vacuum. Next, benzylic bromide **6**

(457 mg, 2.32 mmol) was added as a solution in diethyl ether (23 mL), and the resulting suspension was maintained at room temperature with stirring for 2 h. Following this time, ketone **5** (870 mg, 3.47 mmol) was added to the reaction as a solution in diethyl ether (5 mL). The reaction was maintained for 1 h with stirring at room temperature and then quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). Water (10 mL) was added and the biphasic solution was extracted with diethyl ether (25 mL). The organic phase was washed sequentially with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude isolate was purified by flash chromatography (30 : 1 petroleum ether : ethyl ether eluent) to yield tertiary alcohol **12** (556 mg, 65% yield): R_f 0.38 (10 : 1 hexanes : ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.8, 1.1 Hz, 1H), 7.18–7.11 (m, 2H), 7.08–7.00 (m, 2H), 6.93 (dd, J = 17.3, 10.9 Hz, 1H), 6.88–6.81 (m, 2H), 6.78 (dd, J = 7.7, 1.1 Hz, 1H), 5.51 (dd, J = 17.3, 1.4 Hz, 1H), 5.13 (dd, J = 10.9, 1.4 Hz, 1H), 4.42 (s, 1H), 3.37 (d, J = 13.4 Hz, 1H), 3.31 (d, J = 13.4 Hz, 1H), 1.56 (s, 3H), 1.08 (s, 9H), 0.42 (s, 3H), 0.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.22, 138.25, 135.68, 135.53, 135.46, 132.02, 128.16, 127.97, 127.22, 126.77, 125.89, 121.24, 118.46, 115.23, 76.45, 44.79, 27.07, 26.30, 18.70, –3.36, –3.64; IR (NaCl/film) 3532, 2931, 2859, 1598, 1577, 1485, 1445, 1255, 1234, 1052, 906, 838, 781, 753 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{23}H_{33}O_2Si$ $[M+H]^+$: 369.2250, found 369.2260.

Diol 4

To a solution of silyl ether **12** (475 mg, 1.29 mmol) in THF (3 mL) was added TBAF (1 M solution in THF, 1.41 mL, 1.42 mmol). The resulting solution was then maintained with stirring at room temperature until silyl ether **12** was consumed by TLC analysis (about 1 h). The reaction was diluted with water (10 mL) and then extracted with diethyl ether (25 mL). The organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried with $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (12 : 1 → 10 : 1 hexanes : ethyl acetate eluent) to yield diol **4** (291 mg, 89% yield): R_f 0.22 (10 : 1 hexanes : ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.55 (dd, J = 7.7, 1.3 Hz, 1H), 7.33–7.25 (m, 1H), 7.25–7.14 (m, 2H), 7.12–6.96 (m, 3H), 6.89 (dd, J = 8.1, 1.3 Hz, 1H), 6.87–6.79 (m, 1H), 5.63 (dd, J = 17.3, 1.3 Hz, 1H), 5.29 (dd, J = 10.9, 1.3 Hz, 1H), 3.36 (d, J = 13.9 Hz, 1H), 3.20 (d, J = 13.9 Hz, 1H), 2.51 (s, 1H), 1.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.81, 138.43, 135.12, 133.51, 132.13, 129.72, 129.09, 127.53, 127.46, 126.37, 126.12, 119.54, 117.76, 116.21, 79.13, 44.54, 28.12; IR (NaCl/film) 3306, 1618, 1582, 1491, 1453, 1374, 1293, 1237, 1154, 1095, 1036, 989, 914, 865, 752 cm^{-1}; HRMS (FAB+) m/z calc'd for $C_{17}H_{17}O$ $[M+H]^+$–H_2O: 237.1279, found 237.1268.

Tetracycle 14

A flame-dried reaction flask was charged with $PdCl_2$ (6.9 mg, 0.0393 mmol) and $CuCl_2$ (5.3 mg, 0.0393 mmol). THF (1.5 mL) was added followed by diol **4** (50 mg, 0.197 mmol) as a solution in THF (500 μL). The reaction was placed under an oxygen atmosphere (1 atm) and maintained at room temperature with vigorous stirring until diol **4** was consumed by TLC analysis (about 24 h). Upon completion, the reaction solution was passed through a short column of $MgSO_4$, concentrated under vacuum, and purified by flash chromatography (50 : 1 → 25 : 1 hexanes : ethyl acetate eluent) to yield tetracycle **14** (30.4 mg, 61% yield): R_f 0.41 (10 : 1 hexanes : ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, J = 7.7, 1.3 Hz, 1H), 7.23–7.12 (m, 2H), 7.11–7.02 (m, 2H), 7.02–6.97 (m, 1H), 6.85 (td, J = 7.5, 1.2 Hz, 1H), 6.71 (dd, J = 8.2, 1.1 Hz, 1H), 3.29 (d, J = 16.0 Hz, 1H), 2.95 (d, J = 16.1 Hz, 1H), 1.98 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.06, 135.87, 133.19, 128.20, 128.18, 128.06, 127.42, 126.75, 125.72, 124.58, 120.71, 116.81, 97.66, 73.08, 43.09, 27.62, 26.67; IR (NaCl/film) 2994, 2932, 1607, 1585, 1484, 1452, 1382, 1299, 1275, 1249, 1115, 1081, 978, 899, 879, 760 cm^{-1}; HRMS (MM: ESI-APCI) m/z calc'd for $C_{17}H_{17}O_2$ $[M+H]^+$: 253.1223, found 253.1211.

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Notes and references

1 Joint United Nations Programme on HIV/AIDS; World Health Organization. *AIDS epidemic update: Special report on HIV/AIDS*; December 2006; Geneva, Switzerland, 2006.

2 (*a*) A. A. Johnson, C. Marchand and Y. Pommier, *Curr. Top. Med. Chem.*, 2004, **4**, 1059–1077; (*b*) R. Dayam and N. Neamati, *Curr. Pharm. Des.*, 2003, **9**, 1789–1802; (*c*) M. Witvrouw, B. V. Maele, J. Vercammen, A. Hantson, Y. Engelborghs, E. D. e. Clerq, C. Pannecouque and Z. Bebyser, *Curr. Drug Metab.*, 2004, **5**, 291–304; (*d*) S. D. Young, *Curr. Opin. Drug Disc. Devel.*, 2001, **4**, 402–410; (*e*) D. J. Hazuda, P. Felock, M. Witmer, A. Wolfe, K. Stillmock, J. A. Grobler, A. Espeseth, L. Gabryelski, W. Schleif, C. Blau and M. D. Miller, *Science*, 2000, **287**, 646–650.

3 S. B. Singh, D. L. Zink, D. S. Quamina, F. Pelaez, A. Teran, P. Felock and D. J. Hazuda, *Tetrahedron Lett.*, 2002, **43**, 2351–2354.

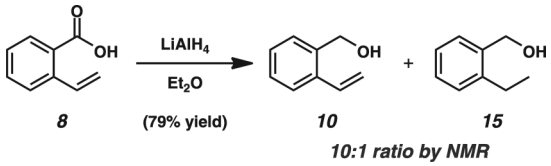
4 (*a*) J. S. Foot, G. M. P. Giblin and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 4441–4444; (*b*) J. S. Foot, G. M. P. Giblin, A. C. Whitwood and R. J. K. Taylor, *Org. Biomol. Chem.*, 2005, **3**, 756–763; (*c*) C. V. Ramana, C. N. Reddy and R. G. Gonnade, *Chem. Commun.*, 2008, 3151–3153.

5 (*a*) S. Krishnan, J. T. Bagdanoff, D. C. Ebner, Y. K. Ramtohul, U. K. Tambar and B. M. Stoltz, *J. Am. Chem. Soc.*, 2008, **130**, 13745–13754; (*b*) Q. Liu, E. M. Ferreira and B. M. Stoltz, *J. Org. Chem.*, 2007, **72**, 7352–7358; (*c*) U. K. Tambar, D. C. Ebner and B. M. Stoltz, *J. Am. Chem. Soc.*, 2006, **128**, 11752–11753; (*d*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *Synlett*, 2006, 3081–3087; (*e*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5970–5978; (*f*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 9552–9553.

6 J. A. Seijas, M. Pilar Vázquez-Tato, C. Entenza, M. Montserrat Martínez, M. Gabriela Ónega and S. Veiga, *Tetrahedron Lett.*, 1998, **39**, 5073–5076.

7 B. Bonnaud, P. Funes, N. Jubault and B. Vacher, *Eur. J. Org. Chem.*, 2005, 3360–3369.

8 All attempts to reduce the acid directly (*e.g.*, with $LiAlH_4$) resulted in significant quantities of the fully reduced product (**15**), lacking the key terminal olefin.



9 T. Murata, S. Sasaki, Y. Takashi, Y. Ikegami, T. Masuda, M. Shimada, T. Shintani, M. Shimazaki, T. B. Lowinger, K. B. Ziegelbauer, K. Fuchikami, M. Umeda, H. Komura, N. U. S. Yoshida, Patent US2004/97563 A1, 2004.
10 For selected examples of palladium(II)-catalyzed oxidations of olefins in alcohols to produce acetals, see: (*a*) N. T. Byrom, R. Grigg and B. Kongkathip, *J. Chem. Soc., Chem. Commun.*, 1976, 216–217; (*b*) J. Tsuji, *Synthesis*, 1984, 369–384; (*c*) P. Perlmutter, W. Selajerern and F. Vounatsos, *Org. Biomol. Chem.*, 2004, **2**, 2220–2228; (*d*) A. M. Balija, K. J. Stowers, M. J. Schultz and M. S. Sigman, *Org. Lett.*, 2006, **8**, 1121–1124; (*e*) J. S. Yadav, S. S. Hossain, M. Madhu and D. K. Mohapatra, *J. Org. Chem.*, 2009, **74**, 8822–8825.