Published in final edited form as:
Bioorg Med Chem Lett. 2012 June 1; 22(11): 3776–3780. doi:10.1016/j.bmcl.2012.04.007.

Bio-inspired synthesis and biological evaluation of a colchicine-related compound library

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Abstract

A bio-inspired investigation of the reactions of substrates of type **1** with VOF_3 and PIFA [phenyliodine(III) bis(trifluoroacetate)] led to a collection of colchicine-like compounds **2–5** and related systems. Biological evaluation revealed that some of the synthesized products had significant cytotoxic properties against the colon cancer cell line HT-29.

Keywords

bio-inspired synthesis; colchicine-like compounds; natural products; oxidative coupling; anti-cancer agents

The continuous unraveling of nature's molecular diversity has led to an impressive number of medications for the treatment of disease.[1,2] Natural products have served directly as therapeutics or lead compounds for the discovery of clinically used drugs[3] as well as myriad of biological tools.[4,5] Important pharmaceuticals originating from natural sources are used in various capacities, including as pain killers, anti-infectives, immuno-suppressants, and anti-cancer drugs.

Colchicine, a natural product used for the treatment of acute gout disease, has been the focus of numerous investigations as a potential anti-cancer drug.[6] Its potent cytotoxicity (IC_{50} = 0.008 μM against HT-29, human colon adenocarcinoma)[7] makes colchicine an intriguing chemotherapeutic candidate. However, a lack of selectivity has prevented it, thus far, from being an approved medication for cancer patients. As part of our program of creating molecular diversity as inspired by natural products and their biosyntheses, we investigated a number of synthetic pathways to colchicine-like and related compounds. Herein we report

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Supplementary data
Supplementary data associated with this with article can be found online, at doi:10.1016/j.bmcl.2012.xx.xxx.

the synthesis of a library of bio-inspired compounds, and their biological evaluation as cytotoxic agents.

Scheme 1 summarizes the postulated biosynthetic pathway leading from dopamine (**I**) and phenol aldehyde (**II**) to demecolcine (**V**) and thence colchicine (**VI**) via (*S*)-autumnaline (**III**) and (*S*)-isoandrocymbine (**IV**). The first two enzymatic transformations of (**I** + **II** to **III**) and (**III** to **IV**) are well understood as a Pictet-Spengler and an oxidative phenol-phenol coupling, respectively.[8] However, the conversion of isoandrocymbine to demecolcine and thence colchicine (**IV** to **V** and **VI**) is more complex and rather speculative (see Scheme 1).[8] These complexities are reflected in the fact that a biomimetic total synthesis of colchicine still has not been reported.[6] Thus, while the non-enzymatic conversion of (**I** + **II** to **III**) has been demonstrated in the laboratory, not all the subsequent steps have been reported as yet by chemical means.[9] Our studies were, therefore, focused on finding conditions to realize useful pathways for the formation of colchicine-like structures and related scaffolds starting from substrates **1** (Figure 1), which are derivatives of autumnaline (**III**). The four possible tetracyclic structural motifs **2–5** were expected to be formed oxidatively from **1**, as shown in Figure 1 (see color code).

Scheme 2 summarizes the results of our investigations of the reaction of the readily available substrates **1a–f** (synthesized by standard methods; see Supplementary data)[8,10] with VOF_3–TFA–TFAA, an approach previously reported by Kupchan and co-workers.[10d,11] At the outset of our work, the potential of this reaction to produce novel molecular diversity was still considered to be high because of the limited number of products and biological data reported by Kupchan *et al.*[10d,11] Indeed, under two different sets of conditions [a) or b)] a variety of additional products were obtained as shown in Scheme 2. Thus, under conditions a) [VOF_3, TFA–TFAA, CH_2Cl_2, 0–25 °C] several new compounds were isolated: **2a** (22% yield from **1a**); **8c** (7% yield) plus **9c** (6% yield) from **1c; 2d** (17% yield) plus **7d′** (5% yield) plus **9d** (7% yield) from **1d; 2e** (46% yield)[10d,11] plus **11a** (27% yield) from **1e**; and **2f** (< 2% yield) plus **7f** (23% yield)[10d,12] plus **8f** (< 2% yield) from **1f**. At lower temperatures, conditions b) [−20 → 0 °C], the VOF_3 reaction yielded compounds **2a** (22% yield) plus **9a** (7% yield) plus **7a** (< 2% yield, this compound was obtained in 17% yield under different conditions, see Scheme 2) from **1a; 2b** (34% yield) plus **7b** (7% yield, this compound was obtained in 19% yield under different conditions, see Scheme 2) from **1b**; and **7e** (11% yield) from **1e**.[10d] Since we were primarily interested in generating molecular diversity rather than any particular compound, no further attempts were made to improve the selectivity of this reaction.

Hoping to synthesize additional novel products from substrate **1e**, we explored its reaction with VOF_3 under three additional sets of conditions [a), b) and c), Scheme 3]. Thus, treatment of **1e** with VOF_3 [TFA–TFAA–CH_2Cl_2, 10:1:100, conditions a)] at 0–25 °C for 3 h furnished scaffolds **10a** (9% yield) and **11a** (17% yield). Carrying out the same reaction in neat TFA–TFAA [75:1, conditions b)] led to the isolation of **2e** in 46% yield and **11a** in 27 % yield. Modifying these conditions further [TFA–TFAA–CH_2Cl_2 10:1:150 for 16 h, conditions c)] afforded **11a** in 49% yield. Derivatives **11b–11j** were prepared from **11a** by standard procedures as summarized in Scheme 3. Compounds **10b** and **11j′** were also formed as shown in Scheme 3, the latter as a major byproduct of the reaction of **11a** with trifluoromethanesulfonic anhydride (Tf_2O).

We then examined the reaction of substrates **1a–f** with phenyliodine(III) bis(trifluoroacetate) (PIFA)[13] from which a number of new molecular scaffolds were isolated as shown in Scheme 4. Thus, exposure of tetrahydroisoquinolines **1a–f** to PIFA in CH_2Cl_2 at 0 → 25 °C led to products **3a** (13% yield) from **1a; 3b** (35% yield) from **1b; 3c** (14% yield) plus *o*-quinone **4c′** (9% yield) from **1c; 3d** (5% yield)[9] plus **4d** (7% yield) from **1d; 3e** (8%

yield)[10d,11] plus **3e′** (6% yield) plus **4e** (< 2% yield) from **1e**; and **3f** (25% yield) from **1f**.[8,9,12,14] Changing the solvent from CH_2Cl_2 to benzene and heating at 80 °C, the PIFA reaction with **1a–f** mostly favors the formation of motif **4**, producing **4a** (12% yield) from **1a; 4b** (< 2% yield) from **1b**, among a complex mixture of other products; **4c** (22% yield) from **1c; 4d** (< 2% yield) from **1d**; and **4e** (10% yield) plus **3e** (< 2% yield) plus **3e′** (< 2% yield) from **1e**. Derivative **4e′** (83% yield) was prepared from **4e** as indicated in Scheme 4. The formation of products **3a–f** is presumed to proceed via either the addition-elimination pathway[13d,e] (intermediate **12a**), or the phenoxenium ion pathway[13d,e] (phenoxenium ion **12b** and its resonance counterpart - carbenium ion **12c**) as demonstrated in Scheme 4. The generation of compounds **4a–e** is assumed to proceed through fleeting intermediates **12b, 12c** and **12d** (1,4-quinomethine) (Scheme 4).

Compounds **5a–e** were prepared from isoquinoline **13**[15] as summarized in Scheme 5. Thus, benzylation or methylation of **13** (K_2CO_3, BnBr or MeI) and subsequent reduction with lithium aluminum hydride (LAH) gave rather labile derivative **14a** or **14b**. Heating the latter compounds in the presence of $HCOOH–H_3PO_4$ [15] led, through presumed iminium species **15**, to **5a** (19% overall yield) from **13, 5c** (38% overall yield) plus **5d** (14% overall yield) from **13**. Acetylation of **5a** and **5d** led to derivatives **5b** (80% yield) and **5e** (70% yield), respectively.

Scheme 6 summarizes the reaction of isoquinoline **13** with PIFA leading, first to the previously mentioned (see Scheme 3) tetracyclic product **11a** (11% yield), and thence to pentacyclic compound **17** (7% yield from **13**). This process is believed to proceed through intermediates **16a, 16b**, and **16c** as depicted in Scheme 6.

Colchicine exerts its cytotoxic activity through tubulin binding that disturbs the tubulin-microtubule equilibrium.[6] As we mentioned before, colchicine is highly potent against the colorectal adenocarcinoma cell line HT-29. The synthesized colchicinoid and related compounds were, therefore, assayed for cytotoxicity against HT-29 cancer cells using the MTT assay [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide]. The so obtained IC_{50} values are shown in Figure 2, together with that found for colchicine (IC_{50} ~ 0.01 μM) for comparison. Compounds **10a, 11a, 11b, 11e, 11f, 11g**, and **11h** exhibited the highest cytotoxic activity in this assay (IC_{50} values = 0.132–0.684 μM, in red). Compounds **2a, 2e, 4c′, 5a, 8c, 10b, 11c**, and **11d** exhibited lower potencies (IC_{50} values = 0.99–9.10 μM, in blue), while the rest of the compounds showed either low activity (IC_{50} values < 50 μM, in black) or their activity was not determined (n.d., in black).

The bio-inspired investigation of the reactions of autumnaline derivatives **1a–f** led to a series of novel colchicine-related compounds. Biological evaluation of these compounds identified several agents with significant cytotoxicity against HT-29 cancer cells. Among them, the most potent ones were compounds **11a, 11b** and **11e–11h**. These results suggest these molecular scaffolds as leads for further studies aiming at new biological tools and potential therapies for the treatment of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Drs. D. H. Huang and L. Pasternack for NMR spectroscopic assistance, Dr. G. Siuzdak for mass spectrometric assistance and Dr. E. Hamel for helpful discussions. Financial support for this work was provided by the Skaggs Institute for Research and the National Institutes of Health, USA (grant AI055475). We are grateful to

the NSF for a predoctoral fellowship (to V. C.), Merck for a postdoctoral fellowship (to R. A. V.), and NIH for a Pathway to Independence Award (K99EB011530; to K. P.).

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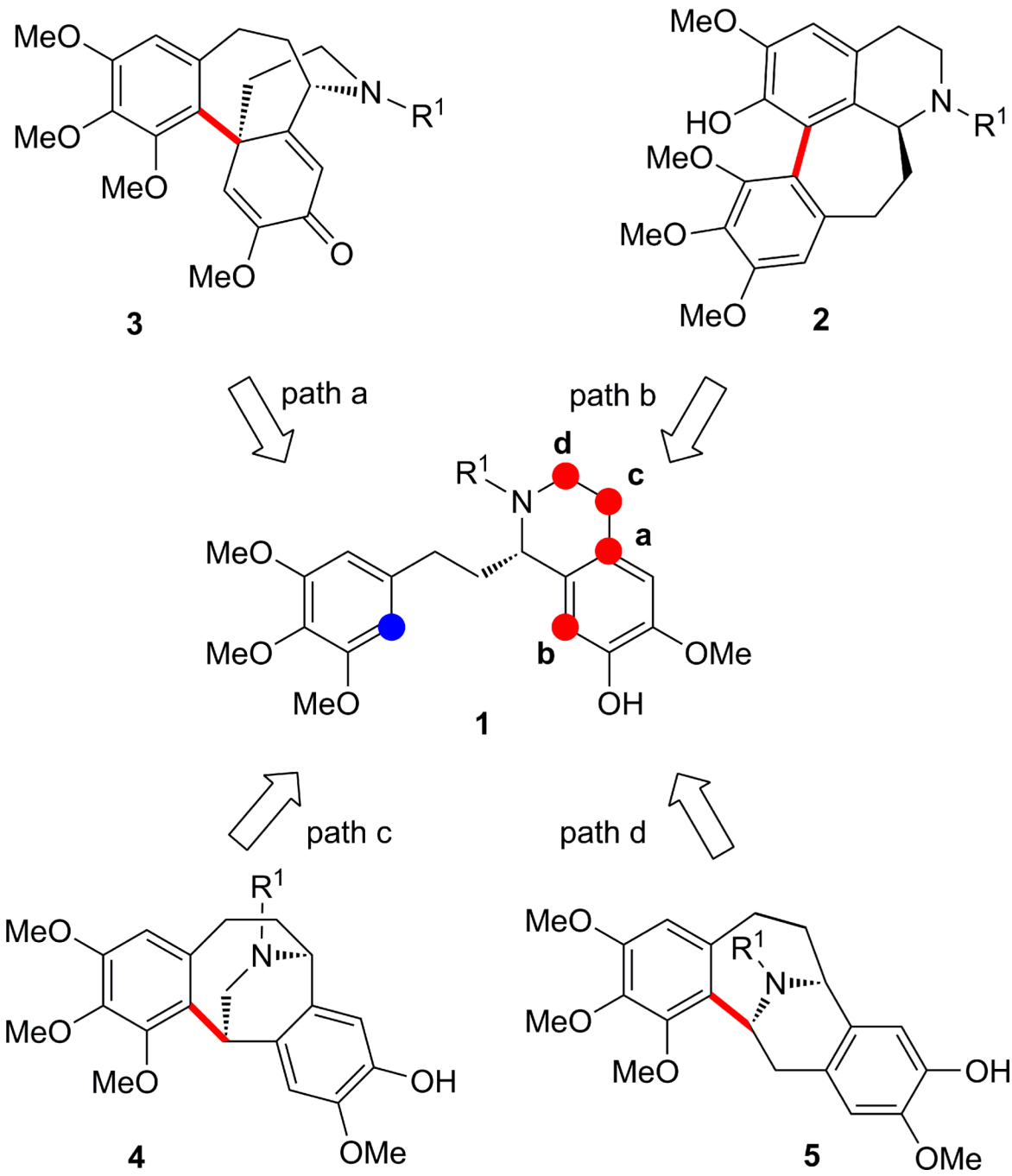


Figure 1.
Possible oxidative pathways depicted in retrosynthetic format to compounds **2–5** from substrates **1**.

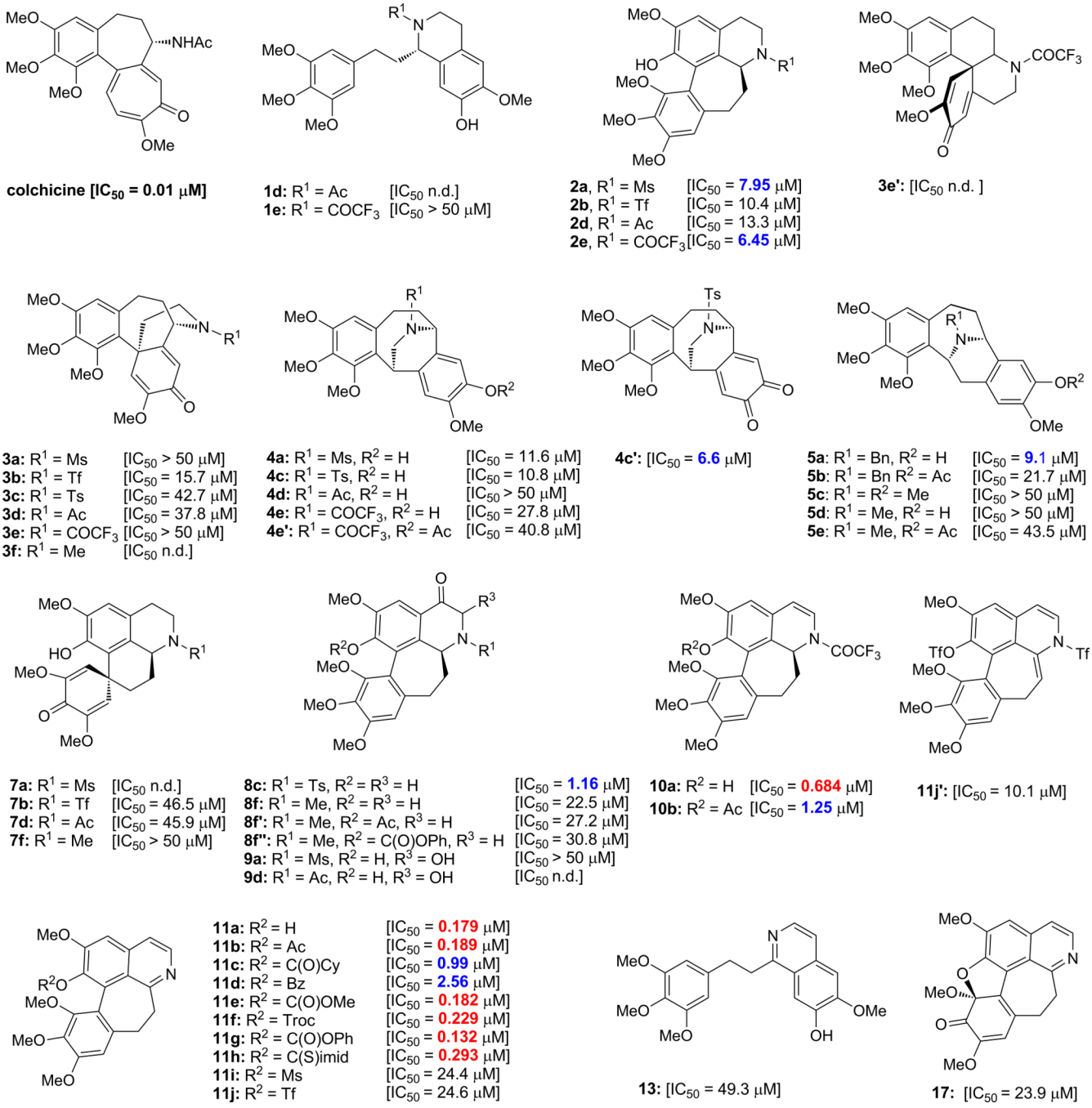
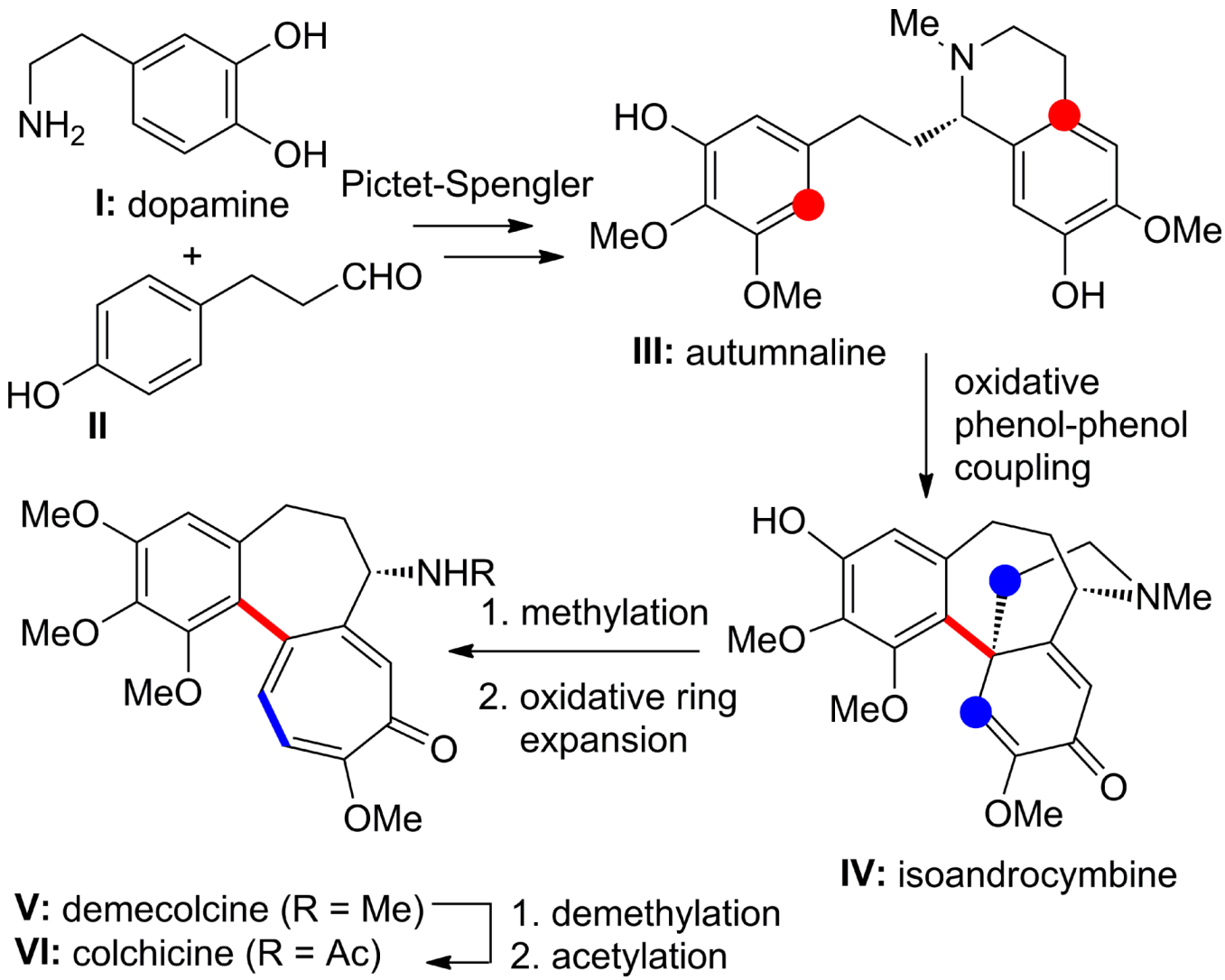


Figure 2.

Cytotoxicity of synthesized compounds against HT-29 cancer cells.a

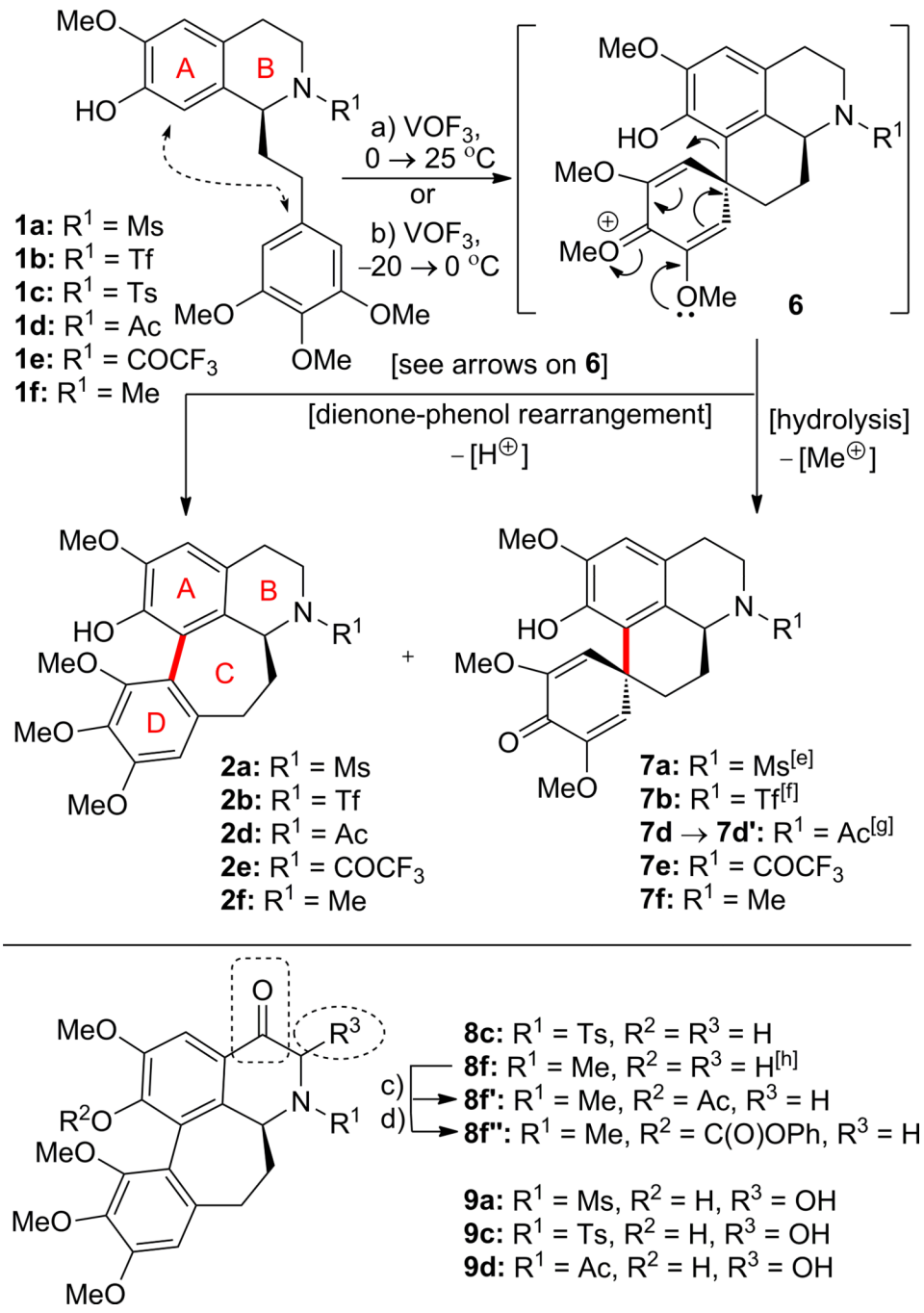
[a] HT-29 cells were grown in RPMI-1640 media supplemented with 10% newborn calf serum (NCS), and maintained at 37 °C with 5% CO_2 and 95% air. Cells were plated in a 96-well plate (5×10^3 cells/well) 24 h prior to incubation with the indicated compound. The media was then replaced with fresh media containing varying concentrations of the indicated compound. Following a 96-hour incubation, MTT (5 mg/mL, 25 μL/well) was added and incubation was continued at 37 °C for 1–2 h (or until formazan crystals were visible in control wells). Media was carefully aspirated and DMSO was added (200 μL/well) to dissolve the purple MTT-formazan crystals. The absorbance of the dissolved formazan was

quantified at 570 nm using UV-Vis plate reader and cell viability was determined as a fraction of absorbance relative to untreated control wells. Each experiment was performed in triplicate and individual data points are presented as averages +/− standard deviation. Figure 2 shows examples of compounds with high (IC_{50} < 1 μM; **red**), medium (IC_{50} < 10 μM; **blue**), low (IC_{50} < 50 μM; black) and negligible (IC_{50} more than 50 μM or n.d. = not determined) anti-HT-29 activity. Bn = benzyl; Bz = benzoyl; Cy = cyclohexyl; Troc = 2,2,2-trichloroethoxycarbonyl; C(S)imid = thionoimidazolide; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.



Scheme 1.

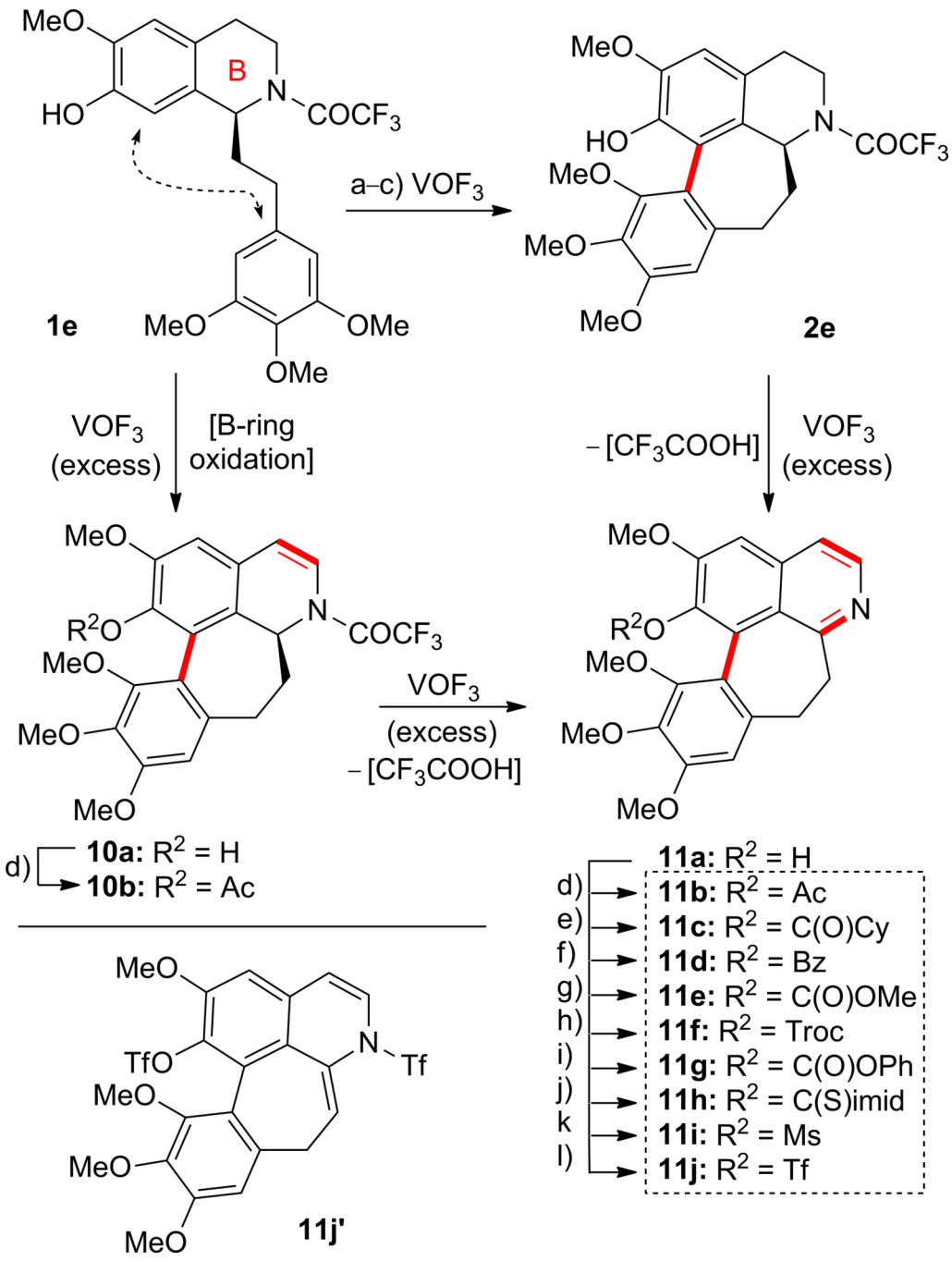
Postulated biosynthesis of demecolcine (**V**) and colchicine (**VI**) from dopamine (**I**) and phenol aldehyde (**II**). Colors indicate atoms joining to form the corresponding C–C bond. The complex skeletal rearrangement from **IV** to **V** or **VI** can be found in Ref. 8.



Scheme 2.

Reactions of compounds **1a–f** with vanadyl trifluoride (VOF_3). Synthesis of compounds **2a,b,d–f, 7a,b,d′,e,f, 8c,f,f′,f″** and **9a,c,d**. Reagents and conditions: a) VOF_3, TFA–TFAA (10:1), CH_2Cl_2, 0 to 25 °C, 0.5–3 h, **1a** → **2a** (22%); **1c** → **8c** (7%) plus **9c** (6%); **1d** → **2d** (17%) plus **7d′** (5%) plus **9d** (7%); **1e** → **2e** (46%) plus **11a** (27%); **1f** → **2f** (< 2%) plus **7f** (23%) plus **8f** (< 2%); b) VOF_3, TFA–TFAA (10:1), CH_2Cl_2, −20 to 0 °C, 0.5–1 h, **1a** → **2a** (22%) plus **9a** (7%) plus **7a** (< 2%); **1b** → **2b** (34%) plus **7b** (7%); **1e** → **7e** (11%); c) AcCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **8f′** (50%); d) PhOC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **8f″** (58%); [e] **1a** → **7a** (17%), −10 °C, 0.3 h; [f] **1b** → **7b** (19%), −30 to −10 °C, 0.8 h; [g] **7d**

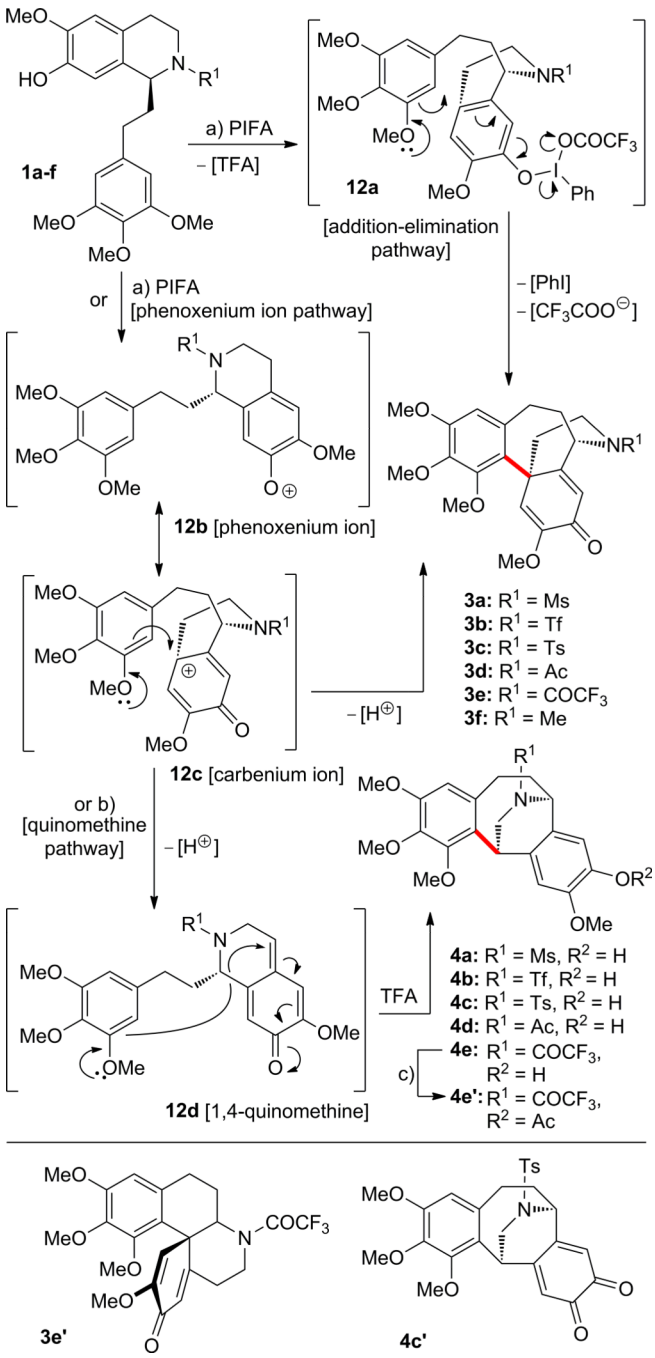
→ **7d′** through C-ring expansion (see Supplementary data); [h] **8f** can be formed from **1f** with PIFA in refluxing benzene or via a skeletal rearrangement from **3f** (Scheme 4) in the presence of a Lewis acid (BF_3•Et_2O in CH_2Cl_2) or a protic acid (*p*-TsOH in AcOH) (see Supplementary data). TFA = 2,2,2-trifluoroacetic acid; TFAA = trifluoroacetic anhydride.



Scheme 3.

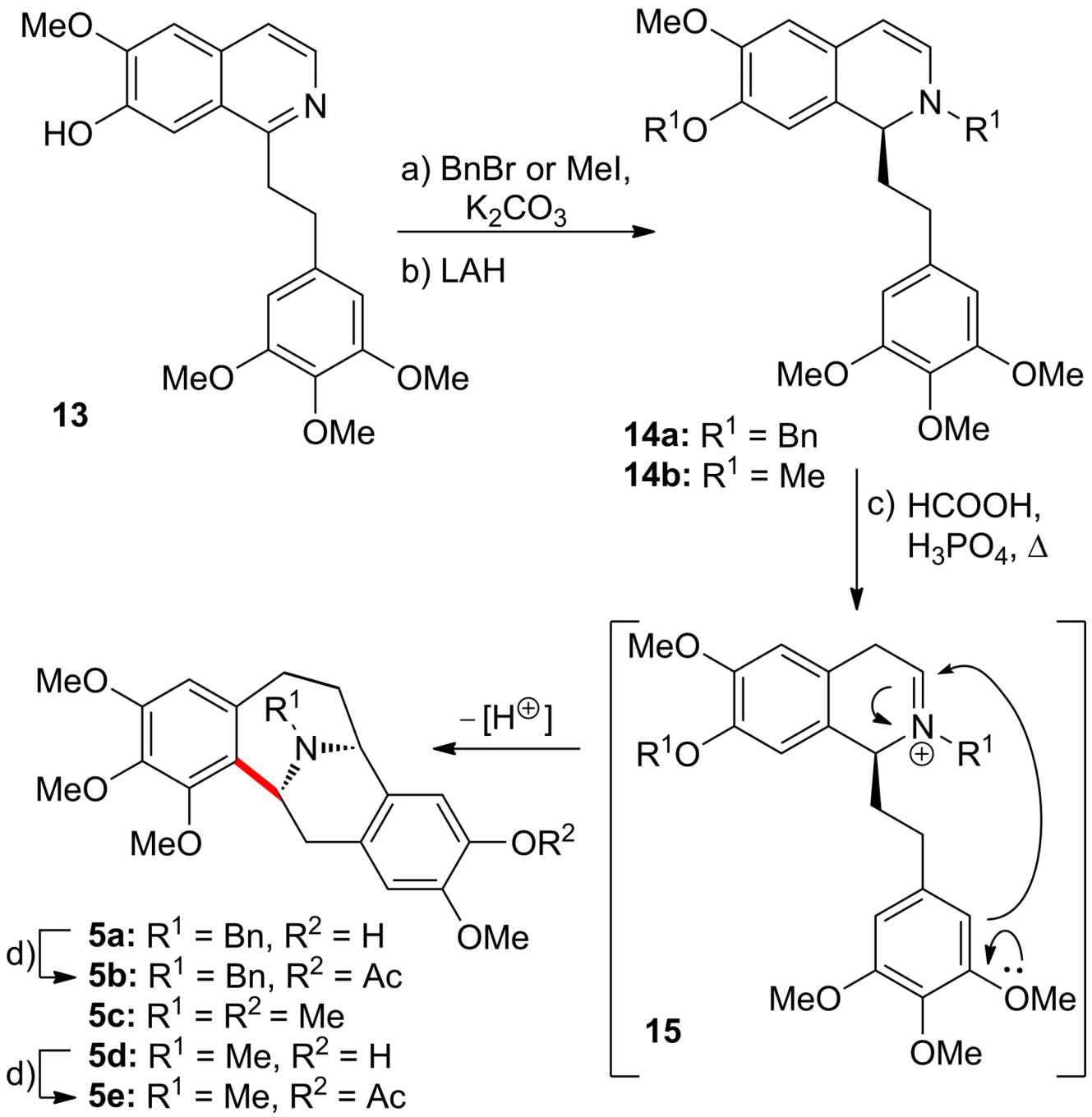
Reaction of compound **1e** with vanadyl trifluoride (VOF_3). Synthesis of compounds **2e, 10a,b, 11a–j,j′**. Reagents and conditions: a) VOF_3, TFA–TFAA–CH_2Cl_2 (10:1:100), 0 to 25 °C, 3 h, **1e** → **10a** (9%) plus **11a** (17%); b) VOF_3, TFA–TFAA–CH_2Cl_2 (75:1:0), 0 to 25 °C, 6 h, **1e** → **2e** (46%) plus **11a** (27%); c) VOF_3, TFA–TFAA–CH_2Cl_2 (10:1:150), 0 to 25 °C, 16 h, **1e** → **11a** (49%); d) AcCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11b** (64%); e) CyC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11c** (88%); f) PhC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11d** (94%); g) MeOC(O)Cl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11e** (54%); h) 2,2,2-trichloroethyl chloroformate, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11f** (77%); i) PhOC(O)Cl, Et_3N, CH_2Cl_2, 0 °C,

0.5 h, **11g** (56%); j) 1,1′-thiocarbonyldiimidazole, Et_3N, CH_2Cl_2, 25 °C, 1 h, **11h** (39%); k) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **11i** (74%); l) Tf_2O, Et_3N, CH_2Cl_2, −78 °C, 0.5 h, **11j** (37%) plus **11j′** (51%). TFA = 2,2,2-trifluoroacetic acid; TFAA = trifluoroacetic anhydride; Cy = cyclohexyl; Bz = benzoyl; Troc = 2,2,2-trichloroethoxycarbonyl; C(S)imid = thionoimidazolide.



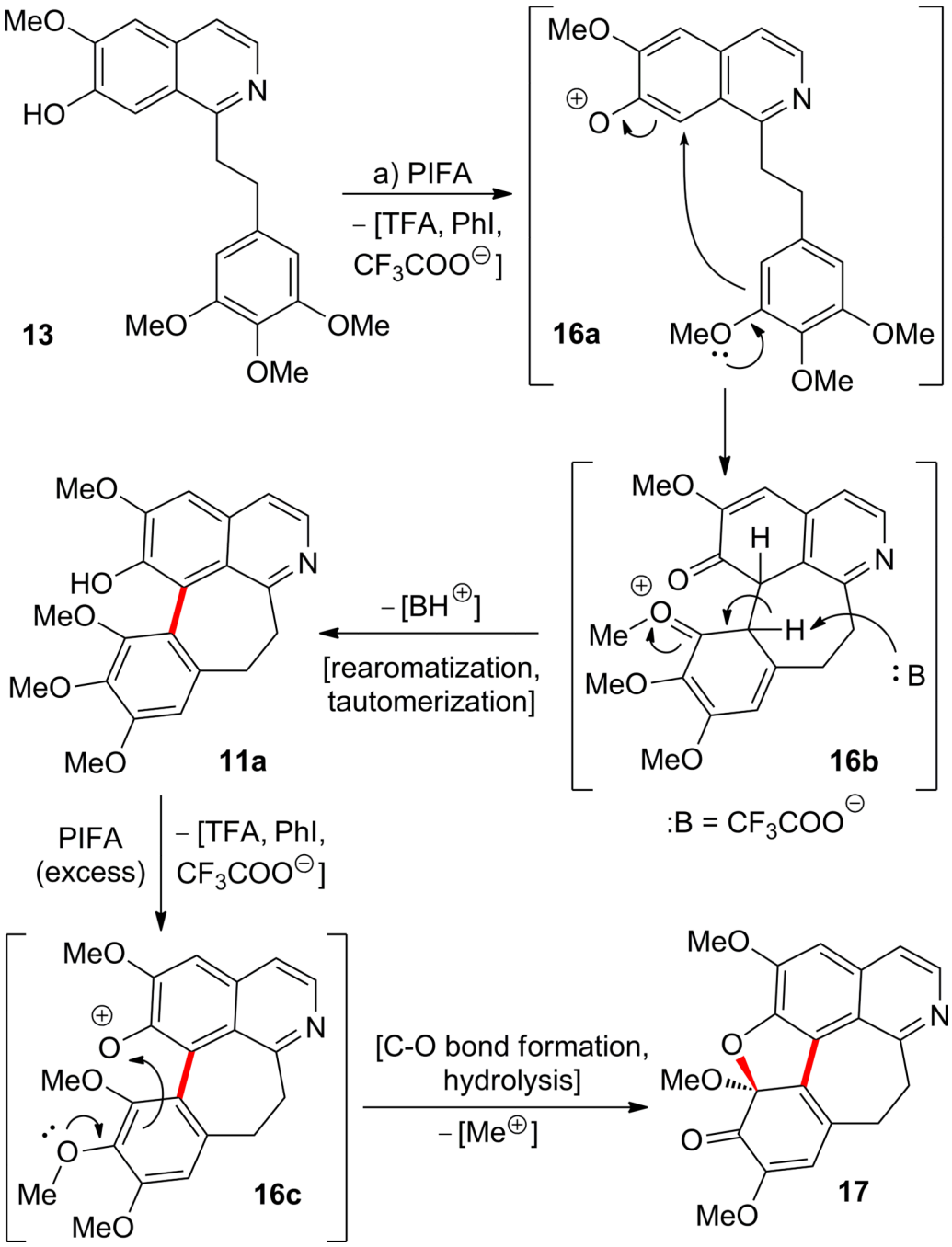
Scheme 4.

Reaction of compounds **1a–f** with phenyliodine(III) bis(trifluoroacetate) (PIFA). Synthesis of compounds **3a–f,e′** and **4a–e,c′,e′**. Reagents and conditions: a) PIFA, CH_2Cl_2, 0 to 25 °C, 0.5–2 h, **1a** → **3a** (13%); **1b** → **3b** (35%); **1c** → **3c** (14%) plus **4c′** (9%); **1d** → **3d** (5%) plus **4d** (7%); **1e** → **3e** (8%) plus **3e′** (6%) plus **4e** (< 2%); **1f** → **3f** (25%); b) PIFA, benzene, 80 °C, 0.5–1 h, **1a** → **4a** (12%), 2.4 h; **1b** → **4b** (< 2%); **1c** → **4c** (22%), 0.5 h; **1d** → **4d** (< 2%); **1e** → **4e** (10%) plus **3e** (< 2%) plus **3e′** (< 2%); c) AcCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **4e′** (83%). TFA = 2,2,2-trifluoroacetic acid.



Scheme 5.

Synthesis of compounds **5a–e**. Reagents and conditions: a) BnBr or MeI, K_2CO_3, acetone, reflux, 2 h; b) $LiAlH_4$, DME, 0 °C, 1 h; c) HCOOH–H_3PO_4 (2:1), 100 °C, 7–20 h, **13** → **5a** (19%); **13** → **5c** (38%) plus **5d** (14%); d) AcCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, **5b** (80%); **5e** (70%). Bn = benzyl; DME = 1,2-dimethoxyethane.



Scheme 6.

Reaction of isoquinoline **13** with PIFA. Preparation of compound **17** and proposed mechanism of its formation from **13** via **11a**. Reagents and conditions: a) PIFA, CH_2Cl_2, 0 to 25 °C, 1 h, **11a** (11%) plus **17** (7%). TFA = 2,2,2-trifluoroacetic acid.