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Synthesis and Biological Evaluation of New Paclitaxel Analogs and Discovery of Potent Antitumor Agents

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Abstract

Reaction of 10-deacetylbaccatin III (**III**) and its 7-TES derivative (**IV**) with DAST under various conditions resulted in the formation of an array of new fluorinated and non-fluorinated 13-keto taxoid compounds (**2a–4a**) through a vinylogous pinacol-pinacolone rearrangement. Further fluorination of some of these products (**2a**, **3a**) with NFSi or Selectfluor gave additional derivatives. Sodium borohydride reduction of the 13-keto group of these products (**2a**, **2b**, **3a**, **3b**, **4a**, **8**, **9**, **11–14**) led to a series of 9 α -hydroxy taxoid derivatives, which were esterified using the docetaxel side chain employing the corresponding protected β -lactam, followed by deprotection to furnish a library of docetaxol analogs and related compounds. A selected number of synthesized compounds (**7**, **10**, **19a**, **19b**, **21a**, **21b**, **23**, **27**, **29**, **34–36**) were submitted to the National Cancer Institute (NCI) 60 cell line screening program and tested for cytotoxic properties. Taxoids **19a**, **19b**, **21a**, **21b**, **23**, **27**, **29**, **34** and **35** were found to exhibit significant anticancer activity against various cancerous cell lines with **23**, **27**, and **29** being the most potent compounds, demonstrating GI₅₀ values of $\sim$ 5 nM in several assays.

Keywords

10-deacetylbaccatin III; docetaxel analogs; paclitaxel; fluorination; natural products; anticancer agents

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EXPERIMENTAL

Supplementary Information: Includes experimental procedures, selected physical data for the synthesized compounds, and further details of biological assays (pdf and cif files). This material is available free of charge via the Internet at <http://pubs.rsc.org>.

INTRODUCTION

Cancer remains as one of the most devastating diseases of our times with millions of patients suffering from it around the world.^{1–6} Moreover, the disease is on the rise and no organ of the human body is immune to its intrusion. Despite the plethora of anticancer drugs currently available for combating cancer, serious deficiencies still prevail, particularly with regards to their efficacy and safety. These chemotherapeutic agents range from small organic molecules and natural products and their analogs, to antibodies and antibody-drug conjugates.^{7,8}

Among the natural products and their semi-synthetic analogs, paclitaxel (**I**, Fig. 1) and docetaxel (**II**, Fig. 1) are perhaps the most well-known and frequently employed due to their potency, selectivity and novel mechanism of action.^{9–11} Paclitaxel is clinically used in the treatment of breast cancer, advanced ovarian cancer, non-small cell lung cancer, and advanced forms of Kaposi's sarcoma,¹² whereas docetaxel is employed against breast cancer, non-small cell lung cancer, gastric cancer, prostate cancer, and squamous cell carcinoma of the head and neck.^{13–15} Cabazitaxel (Jevtana, **II'**), a recently introduced derivative of docetaxel (docetaxel methylated at C7 and C10 hydroxyl groups), is used to treat hormone-refractory prostate cancer. The latter success underscores the importance of fine-tuning the structures of these agents in order to amplify their selectivity towards specific cancers, a theme that is currently attracting special attention in view of personalized medicine.

A large number of paclitaxel and docetaxel analogs became available over the last three decades leading to a useful body of structure-activity relationships (SARs).^{16–38} Enabled by synthesis, these studies were facilitated by the ready availability of paclitaxel and its precursor 10-deacetylbaccatin III (**III**, Fig. 1). Motivated by the approval of cabazitaxel and the successes in medicinal chemistry resulting from the introduction of fluorine residues into small molecules,³⁹ we initiated a research program directed towards the synthesis of fluorinated and other novel taxoids starting from 10-deacetylbaccatin III (**III**, Scheme 1) and its 7-OTES derivative (**IV**, Scheme 1). The virtues of introducing fluorine atoms into organic molecules have been widely recognized and reported;^{39–44} they include increased metabolic stability (resistance to biochemical degradation), enhanced lipophilicity (logP), and stronger binding affinities, often leading to improved pharmacological properties. It is notable that the current number of clinically used drugs containing one or more fluorine atoms stands at 20–30% and is steadily increasing.^{40, 42}

In this article, we report the results of our investigations on the synthesis and biological evaluation of new taxoids, including a number of fluorinated docetaxel analogs.⁴⁵

RESULTS AND DISCUSSION

Reaction of 10-deacetylbaccatin III (**III**) with DAST

The present study began with 10-deacetylbaccatin III (**III**) and its reaction with the common fluorinating agent (diethylamino)sulfur trifluoride (DAST).⁴⁶ Our intention was to obtain as many fluorinated species as possible for the purposes of converting them, through side chain

attachment, to full docetaxel structures for biological evaluation. The top priority at the initial stage was, therefore, structural elucidation of products rather than yield optimization, the latter being postponed until the properties of the molecule would dictate it.

Thus, and as shown in Scheme 1, reaction of **III** with 2.0 equiv of DAST in THF in the presence of 4 Å MS at -78°C over 3 h [conditions (a), Scheme 1] furnished enone **1a** in 93% yield.⁴⁷ Product **1a** was found to be labile and easily transformed to its apparently more stable isomeric paclitaxel-related form **1b** (red ellipsoid, Scheme 1) on silica gel. This conversion could also be induced by 4-DMAP in THF at ambient temperature in 98% yield [conditions (d)]. For the purposes of further manipulations, compound **1a** was also converted to its 7-OTES derivative **2a** under conditions (c) [Et_3SiCl (5.0 equiv), Et_3N (5.0 equiv), 4-DMAP (0.5 equiv), THF, 0°C , 1.5 h; in 74% yield] and thence to the isomerizedtaxoid **2b** under basic conditions [conditions (d), 96% yield]. The latter was also obtained from the previously prepared taxoid **1b** upon silylation in 80% yield [conditions (c)]. Importantly, enone **2a** could also be prepared directly from 7-trimethylsilyl-10-deacetylbaccatin III⁴⁸ (**IV**) (Scheme 1) in 70% yield by exposure of the latter to DAST [2.0–4.0 equiv, THF, 4 Å MS, -78°C , 1–3 h, conditions (a)].

Interestingly, 10-deacetylbaccatin III (**III**) reacted differently with DAST under modified conditions (b) (Scheme 1). Thus, treatment of **III** with 4.0 equiv of DAST in THF: CH_2Cl_2 (5:2), in the presence of 4 Å MS, at -78 to 25°C , over 24 h led to fluorinated enone **3a** in 63% yield accompanied by varying amounts (20%) of elimination product **4a**, inseparable by silica gel chromatography. The formation of product **4a** could be suppressed by diluting the reaction mixture with further amounts of CH_2Cl_2 after the addition of the first 2.0 equiv of DAST and carefully controlling the temperature during the reaction (see ESI for experimental details). Similarly to **1a**, enone **3a** isomerizes to taxoid **3b** in 78% yield under conditions (d) (Scheme 1).

Plausible mechanistic explanations for the reactions mentioned in Scheme 1 are summarized in Scheme 2. Thus, initial reaction of **III** with DAST may produce intermediate **5a** with elimination of HF. This intermediate may then undergo concerted 1,2-*H*-shift and elimination of $\text{Et}_2\text{NS(O)F}$ and F^- to afford protonated species **1a'**, from which observed product **1a** may be formed through the loss of an H^+ . A stepwise process involving the formation of an allylic carbocation for this vinylogous pinacol-pinacolone rearrangement (**5a** $\rightarrow$ **1a**) may also be envisioned. Reaction of hydroxyenone **1a** with further amounts of DAST may then lead, initially to **5b**, and thence to intermediate **5c**, from which all observed products (*i.e.* **3a**, **4a**, and **6**) may be generated^{49–52} as shown in Scheme 2.

Reaction of enones **2a** and **3a** with NFSi and Selectfluor

Having gained access to the new taxoid scaffolds mentioned above, we proceeded to explore their chemistry with additional fluorinating agents. Enones **2a** and **3a** proved to be the most fertile in these pursuits as shown in Schemes 3 and 4, respectively. Thus, treatment of compound **2a** with *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonimide (NFSi)^{53–56} and KHMDS in THF in the presence of 4 Å MS at -78°C [conditions (a), Scheme 3] led to a complex mixture of products from which rather unexpected sulfonate **7** was isolated as a

major product (33% yield), while the expected 14 β -fluorotaxoid **9** was obtained as a minor product (5% yield). In contrast to these results, the reaction of **2a** with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄, or Selectfluor)⁵⁷ under conditions (b) (Scheme 3) [KHMDs (2.0 equiv), Selectfluor (10.0 equiv), THF:DMF (10:1), 4 Å MS, -78 °C, 1–2 h and 25 °C, 1 h] furnished 12 β ,14 β -bis-fluorinated product **9** (24% yield) and varying amounts of 14 β -fluorinated compound **9** (20%) depending on stoichiometry and reaction time.⁵⁸ The latter product is presumed to arise from **2a** via mono-fluorination and enone transposition.

7 α -Fluoroenone **3a** also entered a number of interesting reactions with NFSi and Selectfluor (Scheme 4). Thus, treatment of **3a** with NFSi under conditions (a) [KHMDs (2.2 equiv), NFSi (3.0 equiv), THF, 4 Å MS, -78 °C, 1 h and 25 °C, 1 h] furnished 7 α -fluoro vinyl sulfonate **10** (24% yield) mirroring the reaction of its 7-OTES counterpart **2a** (Scheme 3). On the other hand, reaction of **3a** with Selectfluor under conditions (b) [KHMDs (2.0 equiv), Selectfluor (10.0 equiv), THF:DMF (10:1), 4 Å MS, -78 °C, 1–2 h and 25 °C, 1 h] led to 7 α ,14 β -difluoroenone **11** (5% yield) as a minor product (plus trace amounts of compound **12** (2%), presumably arising from contaminant **4a** present in starting material **3a**, see Scheme 1), and 7 α ,10 α -difluoroenone **13** (17% yield). Further treatment of the latter with excess of Selectfluor under the same set of conditions led to trifluoro enone **14** (mp = 229–230 °C, CH₃Cl/hexanes/EtOAc 10:5:1) in 97% yield. The structure of **14** was unambiguously established by 2D NMR spectroscopic techniques and X-ray crystallographic analysis (see ORTEP drawing, Scheme 4).

Having a variety of rearranged (**2a**, **2b**, **4a**) and fluorinated (**3a**, **3b**, **8**, **9**, **11–14**) taxoids in hand, we pursued their conversion to docetaxel analogs through reduction of their C-13 carbonyl moieties and attachment of the side chain.

Reduction of diketones **2a**, **3a**, and **4**, and preparation of docetaxel analogs **19a**, **19b**, **21a**, **21b** and **23**

As a prelude to the preparation of docetaxel analogs from the dicarbonyl compounds **2a**, **3a**, and **4a**, we subjected the latter to NaBH₄ reduction in the hope that the less hindered 13-carbonyl moiety would be preferentially and selectively reduced to the corresponding 13-hydroxy precursors. Indeed, exposure of **2a**, **3a** and **4a** (as a pure compound or a *ca.* 2:1 of **3a**:**4a** inseparable mixture) to NaBH₄ [2.5 equiv, THF:MeOH (1:2), 0 °C, procedure (a), Scheme 5] led to alcohols **15** (94%), **16** (71%), and **17** [30% yield after chromatographic separation from the concomitantly formed **16** (66% yield)], respectively, all possessing the desired 13 α configuration as shown in Scheme 5. Each of these hydroxy compounds was acylated using procedure (b) (Scheme 5): NaHMDS (2.5 equiv) and β -lactam side chain equivalent (3*R*,4*S*)-3-triethylsilyloxy-4-phenyl-*N*-Boc-2-azetidinone (**V**) (5.0–10.0 equiv) to afford 7,2'-bis-silylated-4-acetoxy products **18a** (53% yield), **20a** (53% yield), 2'-silylated-4-acetoxy-^{7,8} product **22** (31% yield) or 7,2'-bis-silylated-4-deacetyl products **18b** (60% yield), and **20b** (52% yield), depending on the conditions employed (see ESI). These compounds were then desilylated by exposure to conditions (c) (Scheme 5): aqueous HCl, THF:MeOH (1:2), 0 °C, leading to docetaxel analogs **19a** (83% yield), **19b** (89% yield), **21a** (96% yield), **21b** (73% yield), and **23** (94% yield). The absolute stereochemical

configurations of **19a** (mp = 178–181 °C, CH₃CN) and **21a** (mp = 233–235 °C, CH₃CN/hexanes/EtOH 10:2:5) were confirmed by X-ray crystallographic analysis (see ORTEP representations of **19a** and **21a**, Scheme 5).

Reduction of diketones **2b** and **3b** and preparation of docetaxel analogs **27** and **29**

In contrast to the smooth reduction of diketones **2a**, **3a**, and **4a** discussed above, the reaction of compounds **2b** and **3b** with NaBH₄ proved to be complicated and low yielding with regards to the desired 13 α -hydroxy products. Thus, and as shown in Scheme 6a, treatment of **2b** with a large excess of NaBH₄ resulted, through a rather sluggish reaction, in the formation of a complex mixture, in which the over-reduced product **24** was detected as the major compound. The same complications arose in the case of fluorinated diketone **3b** (Scheme 6b) which led, upon treatment with excess of NaBH₄, to a complex mixture, in which the desired alcohol **25** (note the retention at the ^{11,12} olefinic bond as contrasted with **24**) was determined to be the predominant product. Unfortunately, neither product (*i.e.* **24** and **25**) could be isolated in pure form by flash chromatography (silica gel), forcing us to employ the crude mixtures in the side chain attachment step. Thus, treatment of the mixtures containing **24** or **25** (see Scheme 6) with NaHMDS and β -lactam **V** at 0 °C as described above [conditions (b)] furnished pure coupling products **26** (24% yield) or **28** (30% yield), respectively, in pure form after chromatographic separation. Desilylation of products **26** and **28** under conditions (c), (Scheme 6) [aq. HCl, THF:MeOH (1:2), 0 °C] led to docetaxel analogs **27** (58% yield) and **29** (89% yield), respectively.

Reduction of diketones **8**, **13** and **14**

Fluorinated diketones **8**, **13** and **14** exhibited interesting reactivity towards NaBH₄ reduction as shown in Scheme 7. Thus, treatment of 12 β ,14 β -difluorodiketone **9** with a large excess of NaBH₄ [THF:MeOH = 1:2, conditions (a)] resulted in the formation of a mixture of 13 α - and 13 β -hydroxyenones **30a** (44% yield) and **30b** (39% yield) (Scheme 7a). Apparently the replacement of the hydrogen atoms at the C-12 and C-14 positions with fluorines influences the stereoselectivity of this reduction (compare **2a** $\rightarrow$ **15**, Scheme 5). Even more interesting was the NaBH₄-mediated reduction of 7 α ,10 α -difluorodiketone **13** (Scheme 7b) which led to 9 α -hydroxyenone **31** (58% yield). In contrast, the reduction of the trifluoro diketone **14** (Scheme 7c) under the same conditions (a) proved sluggish and required Luche conditions (NaBH₄-CeCl₃•7H₂O), leading to 9 β -hydroxyenone **32** (95% yield). The observed reactivity enhancement of the C-9 carbonyl moiety over the C-13 carbonyl group within diketones **13** and **14** may be attributed to the electron-withdrawing properties of the fluorine substituents at C-7 and C-10 carbons adjacent to the former functional group. The opposite stereochemical outcome of this reduction in the case of **14**, as compared to that of diketone **13** (Scheme 7b), is presumably due to the steric effect of the 10 β -fluorine residue in the latter, an outcome observed also in the reduction of **8**, which led partially to reversal of stereoselectivity (see **8** $\rightarrow$ **30a** + **30b**, Scheme 7a).

While these results were interesting on their own right, they precluded the attachment of the docetaxel side chain at the proper position of the products in order to obtain useful analogs for biological evaluation.

Preparation of unusual taxoids **34–36** from **15** and **16**

While optimizing the conditions for the preparation of docetaxel analogs from hydroxy compounds **15** and **16**, we encountered a number of unusual side-products, including compounds **34**, **35** and **6** (Scheme 8). These compounds were of interest not only from the biological point of view, but also for mechanistic considerations of their formation. Speculative pathways for their generation are outlined in Scheme 8. Thus, under the basic conditions (a) employed for the side chain attachment (*i.e.* NaHMDS), the C-13-alkoxide (**33a**) formed from **15** or **16** may undergo intramolecular rearrangement through C-4-acetyl migration as shown in the case of **15** ($R^1 = \beta\text{-OTES}$), or intramolecular enolate formation as shown in the case of **16** ($R^1 = \text{F}$) to afford acetate **33b** or enolate **33d**, respectively. The former may also rearrange to enolate **33c**. All three reactive species (*i.e.* **33c**, **33b**, and **33d**) may then react with β -lactam **V** to afford the corresponding esters, which upon acid-induced desilylation lead to compounds **34** (39% overall yield from **15**), **35** (12% overall yield from **15**), and **36** (16% overall yield from **16**), respectively as shown in Scheme 8. The absolute configuration of **34** (mp = 161–163 °C, hexanes/EtOAc 10:1) was confirmed by X-ray crystallographic analysis (see ORTEP representation, Scheme 8).

Biological evaluation of selected compounds

Selected compounds from those synthesized and described above, including sulfonates **7**, **10**, docetaxel analogs **19a**, **19b**, **21a**, **21b**, **23**, **27**, **29** and side-products **34–36** were submitted to the NCI 60 cell line screening program.⁴⁵ Initial one-dose screening (at 10 μM conc.) revealed that sulfonates **7**, **10** and 7 α -fluorinated compound **36** possessed weak cytotoxicity (Fig. 2). Specifically, sulfonate **7** demonstrated moderate results, however, not sufficient for the five-dose screening [98% growth inhibition (GI) for HOP-92 (non-small cell lung cancer) and 8% lethality for A498 (renal cancer)]. 7 α -Fluorinated sulfonate **10** was less active [76% growth inhibition (GI) for MDA-MB-435 (melanoma), 66% growth inhibition for HT29 (colon cancer), and RPMI-8226 (leukemia)]. Compound **36** was the least active, suppressing the growth of CNS cancer cell line (SNB-75) by only 33%. While these activities did not warrant further investigation of the compounds mentioned above, those of the remaining did.

Thus, because of their significant potencies against numerous tumor cell lines, docetaxel analogs **19a**, **19b**, **21a**, **21b**, **23**, **27**, **29**, **34**, and **35** were advanced to the five-dose screening stage, revealing more details about their cytotoxicities as depicted in Fig. 2 [the most potent compounds are shown in boxes (*e.g.*, **23**, **27**, and **29**); the highest potencies are emphasized in red (less than 5 nM) and bold black (from 10 to 100 nM)]. Specifically, analogs **23**, **27**, and **29** demonstrated very low GI₅₀ values (less than 5 nM) against most of the 60 cell lines tested: for **23** [for most of the leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer cell lines GI₅₀ < 5 nM]; for **27** [for many of the leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, prostate cancer, and breast cancer cell lines GI₅₀ < 5 nM]; for **29** [CNS cancer (SNB-75) GI₅₀ < 5 nM; melanoma (MDA-MB-435) GI₅₀ < 5 nM and (SK-MEL-5) GI₅₀ = 7 nM; renal cancer (RXF 393) GI₅₀ = 11 nM; breast cancer (HS 578T) GI₅₀ = 7 nM]. Taxoids **19a**, **19b**, **21a**, and **21b** showed moderate cytotoxicity

(GI₅₀ values vary from 10 to 100 nM). In particular, for **19a** [for most of the leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer cell lines GI₅₀ = 10 nM]; for **19b** [leukemia (HL-60(TB)) GI₅₀ = 184 nM; colon cancer (HT29) GI₅₀ = 188 nM; CNS cancer (SNB-75) GI₅₀ = 25 nM; melanoma (MDA-MB-435) GI₅₀ = 76 nM; breast cancer (MCF7) GI₅₀ = 188 nM and (HS 578T) GI₅₀ = 137 nM]; for **21a** [CNS cancer (SNB-75) GI₅₀ = 10 nM; melanoma (MDA-MB-435) GI₅₀ = 13 nM; renal cancer (RXF 393) GI₅₀ = 24 nM; breast cancer (HS 578T) GI₅₀ = 21 nM and (MDA-MB-468)] GI₅₀ = 18 nM]; and for **21b** [non-small cell lung cancer (NCI-H460) GI₅₀ = 210 nM; colon cancer (HT29) GI₅₀ = 259 nM; CNS cancer (SNB-75) GI₅₀ = 87 nM; melanoma (MDA-MB-435) GI₅₀ = 144 nM; breast cancer (MCF7) GI₅₀ = 295 nM]. Analogs **34** and **35** exhibited low cytotoxicities (GI₅₀ = 500 nM for most of the 60 cell lines) as shown in Fig. 2. For further details of the cytotoxicity data see <http://dtp.nci.nih.gov/>.

CONCLUSION

An exploration of the reactivity of the readily available taxoid 10-deacetylbaccatin III towards various fluorinating reagents led to a number of novel baccatin III derivatives, some of which were successfully converted to docetaxel analogs through reduction and side chain attachment. Biological evaluation of these analogs at NCI employing their 60 cell line screening assays led to the identification of a number of highly potent compounds against several cancerous cell lines (*i.e.* **23**, **27**, and **29**; GI₅₀ = 5 nM). These results indicate that oxygenation at C-7 and C-10 of the taxoid family is not necessary for biological activity. They also suggest that some of the reported compounds warrant further investigation aiming at their development as personalized medicines for the treatment of certain cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

DAST	(diethylamino)sulfurtrifluoride
TES	triethylsilyl
MS	molecular sieves
THF	tetrahydrofuran

4-DMAP	4-(dimethylamino)pyridine.
KHMDS	potassium bis(trimethylsilyl)amide
NFSi	<i>N</i> -fluorobenzenesulfonimide
DMF	<i>N,N</i> -dimethylformamide
NaHMDS	sodium bis(trimethylsilyl)amide
PTLC	preparative thin-layer chromatography

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Fig. 1.
Structures of paclitaxel (**I**), docetaxel (**II**), cabazitaxel (**II'**), and 10-deacetylbaccatin III (**III**). Bz = benzoyl; Ac = acetyl; Ph = phenyl.

Fig. 2.

Cytotoxicities of chosen synthesized taxoids against selected cancer cell lines (NCI). For experimental details and definitions, please use the following weblink: (<http://dtp.nci.nih.gov/branches/btb/ivclsp.html>). GI_{50} = growth inhibition of 50%, i.e. drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation; TGI = drug concentration resulting in total growth inhibition; LC_{50} = concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning; SRB

= sulforhodamine B. Units: Molar. Color code: **red** ($GI_{50} < 5$ nM) and **bold black** ($GI_{50} = 10\text{--}100$ nM) numbers indicate high potencies. Average GI_{50} for Taxol for most cell lines varies from 10–35 nM. For further details on all compounds, see Supplementary Information and <http://dtp.nci.nih.gov/> (see Table S1 for compound numbering).

Scheme 1.

Reaction of 10-deacetylbaccatin III (**III**) with DAST. Synthesis of compounds **1a–4a** and **1b–3b**. Reagents and conditions: a) DAST (2.0 equiv), THF, 4 Å MS, -78°C , 3 h, **III** → **1a** (93%); **IV** → **2a** (70%); b) DAST (4.0 equiv), THF:CH₂Cl₂ (5:2), 4 Å MS, $-78 \rightarrow 25^{\circ}\text{C}$, 24 h, **III** → **3a** (63%), plus **4a** (20%); c) Et₃SiCl (5.0 equiv), Et₃N (5.0 equiv), 4-DMAP (0.5 equiv), THF, 0°C , 1.5 h, **1a** → **2a** (74%); **1b** → **2b** (80%); d) 4-DMAP (2.5 equiv), THF, 4 Å MS, 25°C , 20–24 h, **1a** → **1b** (98%); **2a** → **2b** (96%); **3a** → **3b** (78%). DAST =

(diethylamino)sulfurtrifluoride; TES = triethylsilyl; MS = molecular sieves; THF = tetrahydrofuran; 4-DMAP = 4-(dimethylamino)pyridine.

Scheme 2.

Preparation of compounds **3a**, **4a**, and **6** and proposed mechanism for their formation.

Reagents and conditions: see Scheme 1 for a) and b).

Scheme 3.

Fluorination of **2a** with NFSi and Selectfluor. Synthesis of compounds **7–9**. Reagents and conditions: a) KHMDS (2.2 equiv), NFSi (3.0 equiv), THF, 4 Å MS, -78°C , 1 h and 25°C , 1 h, **2a** $\rightarrow$ **7** (33%), plus **9** (5%); b) KHMDS (2.0 equiv), Selectfluor (10.0 equiv), THF:DMF (10:1), 4 Å MS, -78°C , 1–2 h and 25°C , 1 h, **2a** $\rightarrow$ **9** (24%), plus **9** (20%). KHMDS = potassium bis(trimethylsilyl)amide; NFSi = *N*-fluorobenzenesulfonimide; Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); DMF = *N,N*-dimethylformamide.

Scheme 4.

Fluorination of $\mathbf{3a}$ with NFSi and Selectfluor . Synthesis of compounds $\mathbf{10}$ – $\mathbf{14}$. Reagents and conditions: a) KHMDS (2.2 equiv), NFSi (3.0 equiv), THF, 4 Å MS, -78°C , 1 h and 25°C , 1 h, $\mathbf{3a} \rightarrow \mathbf{10}$ (24%); b) KHMDS (2.0 equiv), Selectfluor (10.0 equiv), THF:DMF (10:1), 4 Å MS, -78°C , 1–2 h and 25°C , 1 h, $\mathbf{3a} \rightarrow \mathbf{11}$ (5%), plus $\mathbf{12}$ (2%), plus $\mathbf{13}$ (17%); $\mathbf{13} \rightarrow \mathbf{14}$ (97%).

Scheme 5.

Synthesis of compounds **15–17**, **18a–21a**, **18b–21b**, **22** and **23**. Reagents and conditions: a) NaBH_4 (2.5 equiv), $\text{THF}:\text{MeOH}$ (1:2), 0°C , 0.5–3 h, **2a** $\rightarrow$ **15** (94%); **3a** $\rightarrow$ **16** (71%); **3a:4a** (ca. 2:1 by ^1H NMR) $\rightarrow$ **16** (66%), plus **17** (30%); b) NaHMDS (2.5 equiv), **V** (5.0–10.0 equiv), THF , 4 Å MS, 0°C , 40 min (or $-78 \rightarrow 0^\circ\text{C}$, 40 min see ESI for detailed procedure B1, B2, and B3), **15** $\rightarrow$ **18a** (53%); **15** $\rightarrow$ **18b** (60%); **16** $\rightarrow$ **20a** (53%); **16** $\rightarrow$ **20b** (52%); **17** $\rightarrow$ **22** (31%); c) aq. HCl (1.0 M) (excess), $\text{THF}:\text{MeOH}$ (1:2), 0°C , 1–3 h, **18a** $\rightarrow$ **19a** (83%); **18b** $\rightarrow$ **19b** (89%); **20a** $\rightarrow$ **21a** (96%); **20b** $\rightarrow$ **21b** (73%); **22** $\rightarrow$ **23** (94%).

NaHMDS = sodium bis(trimethylsilyl)amide; **V** = (3*R*,4*S*)-3-triethylsilyloxy-4-phenyl-*N*-Boc-2-azetidinone.

Scheme 6.

Stereo- and regioselectivity of the reduction of ketones **2b** and **3b**. Synthesis of compounds **24–29**. Reagents and conditions: a) NaBH₄ (2.5 equiv → large excess), THF:MeOH (1:2), 0 °C, 1–3 h; b) NaHMDS (2.5 equiv), **V** (5.0–10.0 equiv), THF, 4 Å MS, 0 °C, 40 min, **24** (mixture) → **26** (24%); **25** (mixture) → **28** (30%); c) aq. HCl (1.0 M), THF:MeOH (1:2), 0 °C, 1–3 h, **26** → **27** (58%); **28** → **29** (89%).

Scheme 7.

Stereo- and regioselectivity of the reduction of ketones **8**, **13**, and **14**. Synthesis of compounds **30a**, **30b**, **31**, and **32**. Reagents and conditions: a) NaBH_4 (2.5 equiv $\rightarrow$ large excess), THF:MeOH (1:2), 0 $^\circ\text{C}$, 0.5–2 h (or NaBH_4 (large excess), THF:MeOH (1:2), 0 $^\circ\text{C}$, $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (cat.), see ESI), **8** $\rightarrow$ **30a** (44%), plus **30b** (39%); **13** $\rightarrow$ **31** (58%); **14** $\rightarrow$ **32** (95%).

Scheme 8.

Generation of compounds **34–36** and postulated mechanism for their formation from **15**, **16** and **V**. Reagents and conditions: a) NaHMDS (2.0–3.0 equiv), -78°C , 1 h, then b) **V** (5.0–10.0 equiv), THF, -78°C , 0.5 h and 0°C , 0.5 h, see ESI for detailed procedures B2 and B3; then PTLC, followed by c) aq. HCl (1.0 M) (excess), THF:MeOH (1:2), 0°C , 1–3 h, (yields reported over 3 steps), **15** $\rightarrow$ **34** (39%), plus **35** (12%); **16** $\rightarrow$ **36** (16%). PTLC = preparative thin-layer chromatography.