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**[BIS(TRIFLUOROACETOXY)IODO]*p*-NITROBENZENE AND [BIS(TRIFLUOROACETOXY)IODO]PENTAFLUOROBENZENE AS LEAD REAGENTS FOR THE DIRECT RING CONTRACTION OF LACTAMS TO PYRROLIDINES**

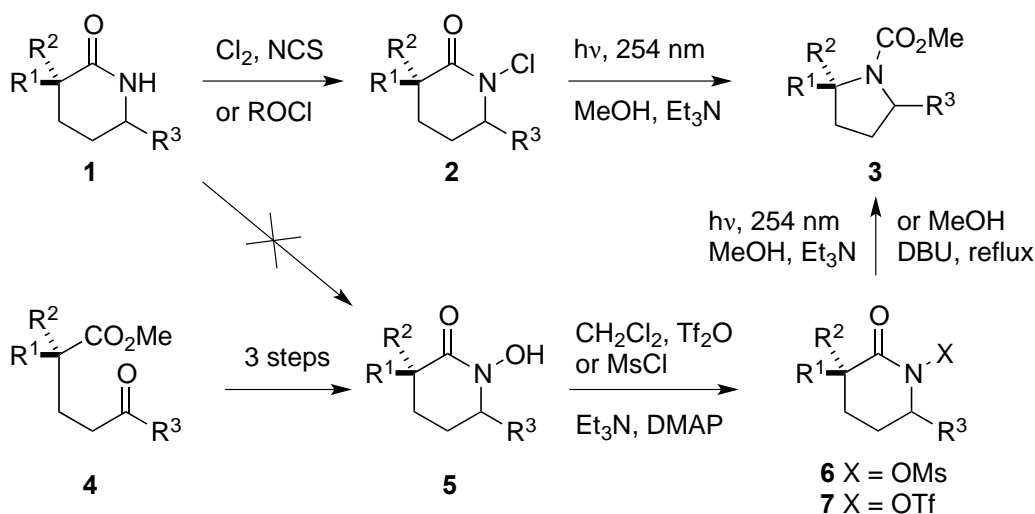
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**Abstract** – Two  $\lambda^3$ -iodanes, namely [bis(trifluoroacetoxy)iodo]*p*-nitrobenzene and [bis(trifluoroacetoxy)iodo]pentafluorobenzene, were used to effect the direct ring-contraction of lactams to pyrrolidines. Intense reaction optimization was necessary but only  $\alpha,\alpha$ -disubstituted lactams succumbed to our efforts thus far.

**INTRODUCTION**

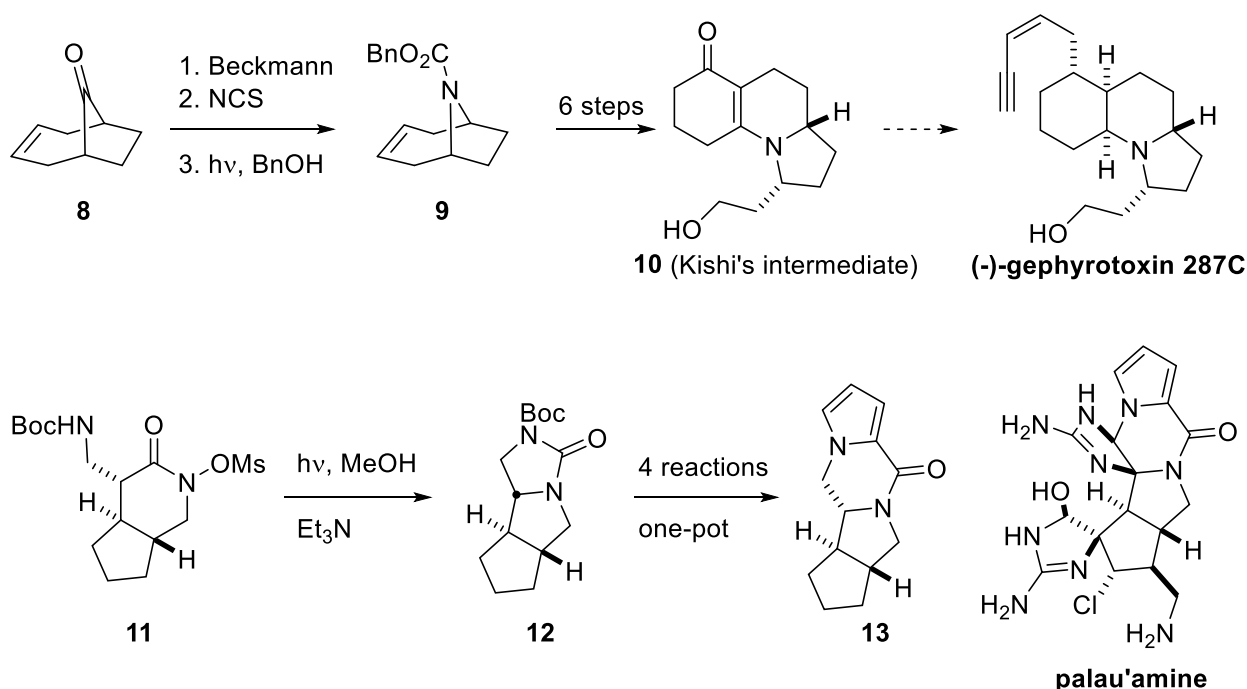
We have developed several procedures for the ring-contraction of *N*-chlorolactams and derivatives of cyclic hydroxamic acids (Scheme 1).<sup>1</sup> This rearrangement is related to the well-known Lossen rearrangement, but it is unique in scope.<sup>2</sup> Indeed, secondary amides and lactams and their derivatives are out-of-bounds for the Lossen-type rearrangements,<sup>3</sup> while our procedures are inefficient with acyclic amide derivatives.<sup>1a</sup>



Scheme 1. Ring-contraction of *N*-chlorolactams or derivatives of hydroxamic acids

In a nut shell: *N*-chlorolactams **2** are conveniently prepared from lactams **1** but give low to moderate yields of the rearranged products **3** under UV irradiation; *N*-mesyloxylactams **6** give the best yields of products **3** all-around, also under UV irradiation, but  $\alpha$ -unsubstituted *N*-mesyloxylactams (**6**,  $R^1 = R^2 = H$ ) remain problematic substrates; finally, *N*-trifloxylactams **7** rearrange thermally in the presence of base and in this case,  $\alpha$ -unsubstituted *N*-trifloxylactams (**7**,  $R^1 = R^2 = H$ ) actually work best. However, both the *N*-mesyloxy and *N*-trifloxylactams suffer from the impracticality of obtaining hydroxamic acids **5** directly from the oxidation of lactams **1**.<sup>4</sup> Hydroxamic acids are usually obtained from the corresponding ketoester **4**.

We have applied the photochemical ring-contraction of *N*-chlorolactams and *N*-mesyloxylactams to the synthesis of natural products (Scheme 2). Bicyclic ketone **8** was converted to azabicyclo[4.2.1]nonane **9** by a short sequence and subsequently to a non racemic form of Kishi's intermediate **10**, which has been used to prepare (-)-gephyrotoxin 287C.<sup>5a</sup> Recently, we used the power of the photochemical rearrangement of *N*-mesyloxylactams to generate the highly strained *trans* cyclopenta[*c*]pyrrolidine **12**, a core fragment of the complex alkaloid palau'amine, from a less strained *trans* cyclohexa[*d*]pyrrolidine **11**.<sup>5b</sup>

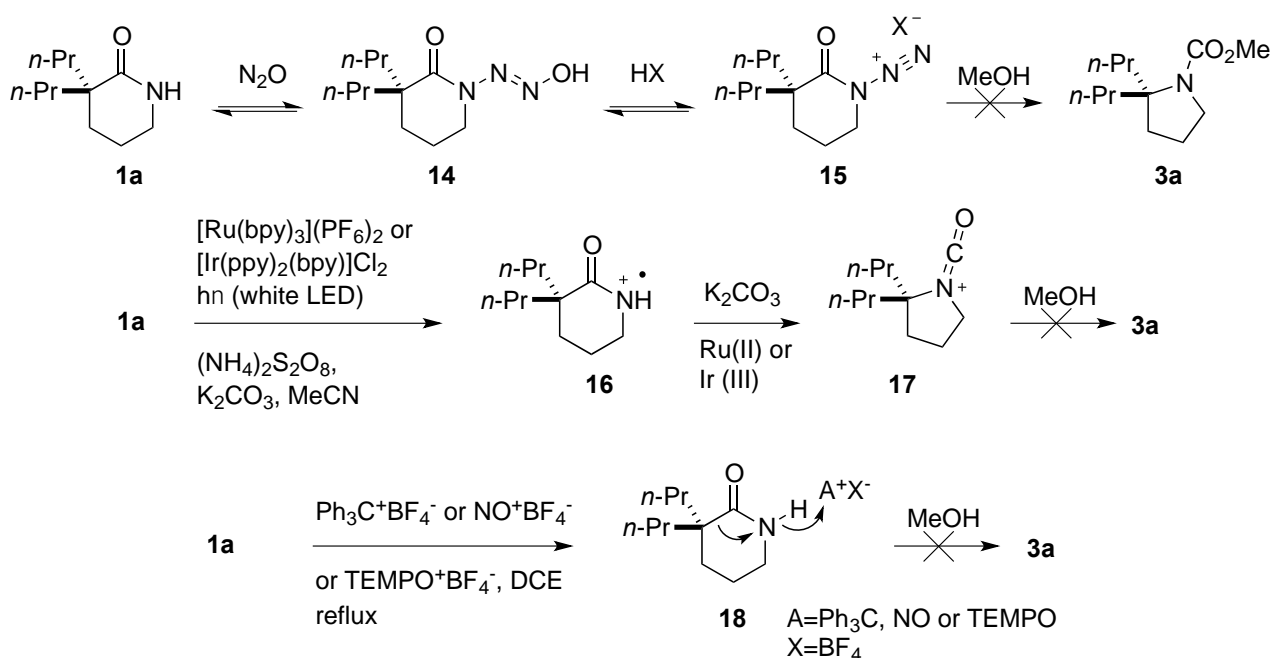


Scheme 2. Applications of the ring-contraction to the synthesis of natural products

## RESULTS AND DISCUSSION

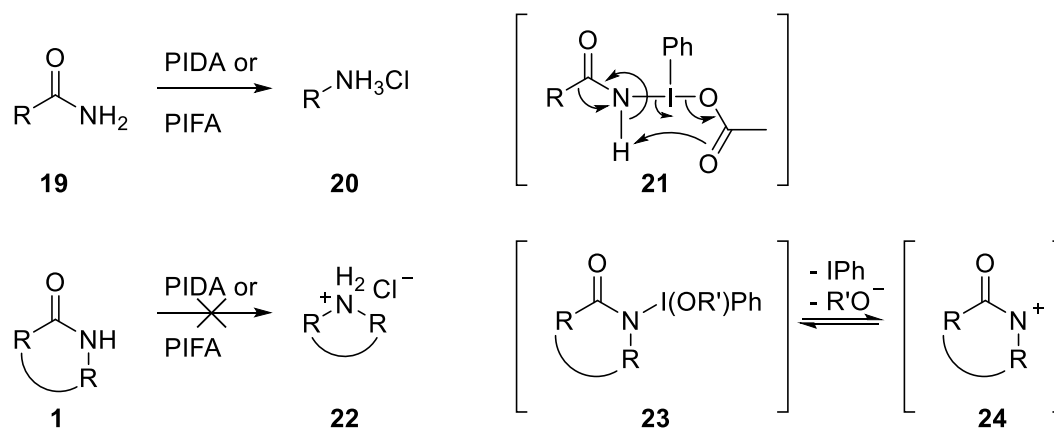
The lack of effective methods to oxidize lactams to hydroxamic acids is a damper on the overall synthetic usefulness of the ring-contraction strategy. The oxidation of lactams or the direct ring-contraction of lactams to carbamates are thus worthwhile goals, which we are pursuing. We have not been successful so

far in finding a solution to the former, despite trying several oxidation methods. We explored several ideas to achieve the latter, including the treatment of lactam **1a** with  $N_2O$  in acidic conditions in the hope of generating *in situ* a diazonium salt **15**, which would rearrange thermally to pyrrolidine **3a**, as well as the photoredox catalysis shown in Scheme 3.<sup>6</sup> None of these experiments yielded the desired compound **3a**. Finally, hydride acceptors were tested on lactam **1a** to no avail, as only starting material was recovered.

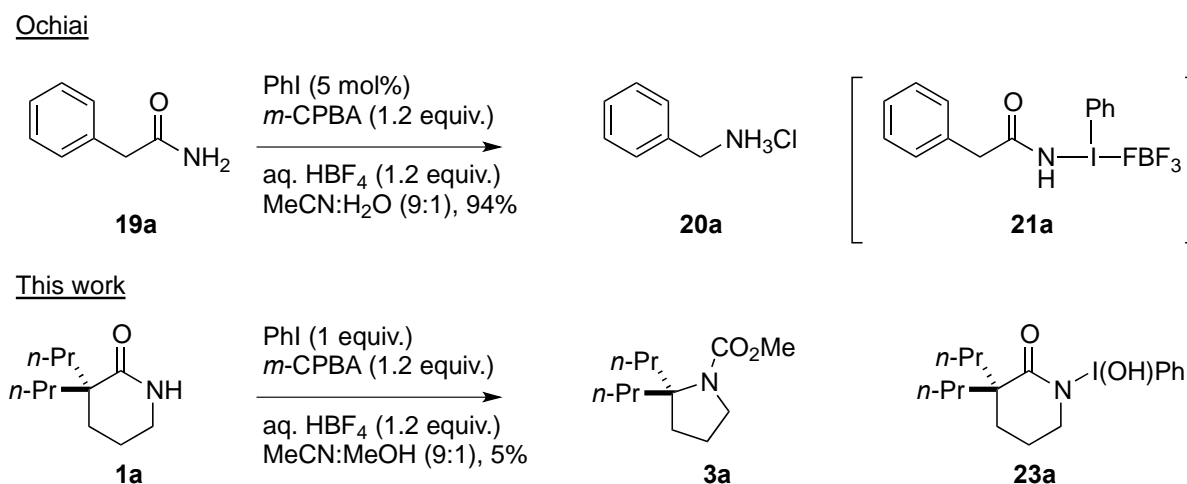


Scheme 3. Unsuccessful explorations of the direct ring-contraction of lactams

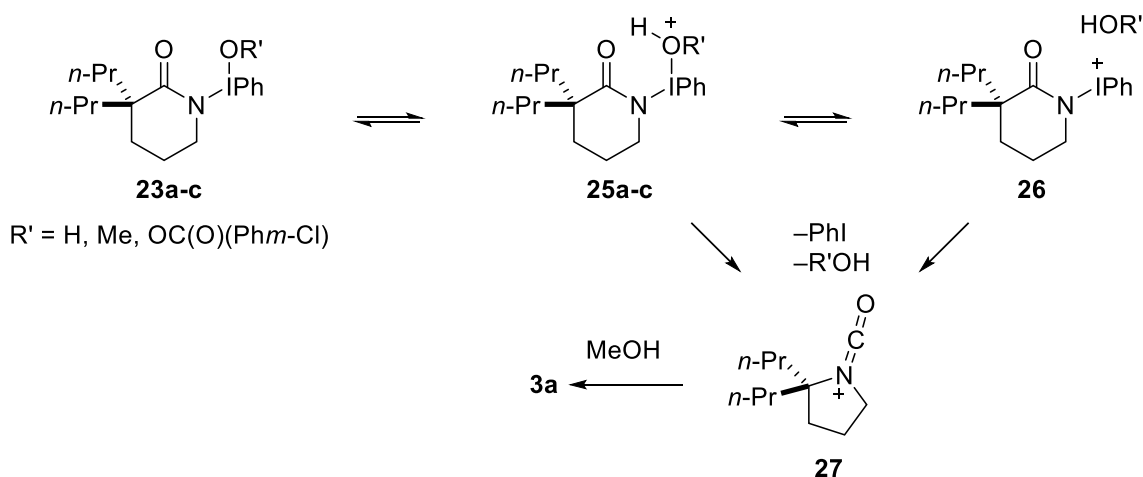
However, we were successful in effecting the desired ring-contraction using  $\lambda^3$ -iodane reagents, after careful optimization.  $\lambda^3$ -Iodanes are powerful oxidizing agents and they have been used for the Hofmann rearrangement of primary amides (Scheme 4).<sup>7</sup> To think that the ring-contraction of **1a** should proceed as easily as the Hofmann rearrangement of **19** would be a misconception. Regardless of the exact nature of the purported intermediate **21**, the departure of the iodide can be accompanied by loss of a proton. Perhaps the rearrangement is concomitant with the departure of the iodide, as proposed by the authors<sup>7</sup> and shown by the mechanistic arrows on structure **21** in Scheme 4. The loss of the proton is essential, but this is not possible with lactams or secondary amides (**1**). Indeed, all examples of iodane(III)-promoted Hofmann rearrangements in the literature involve primary amides (**19**).<sup>7,8</sup> In the case of secondary amides **1**, the departure of iodobenzene in an intermediate like **23** would generate a high energy *N*-acylnitrenium ion **24**. To avoid its formation, the ring-contraction would have to be concomitant with the departure of the iodide. With no deprotonation to accelerate this step, it is expected to be much slower. Indeed, preliminary results with lactam **1a** using these reported methods gave no trace of the desired product **3a**.

Scheme 4.  $\lambda^3$ -Iodane-promoted Hofmann rearrangement of primary Vs secondary amide (**19** Vs **1**)

The reaction conditions reported by Ochiai's group attracted our attention. They achieved the Hofmann rearrangement of amide **19a** to amine **20a** (95%) in strongly acidic conditions using a catalytic amount of iodide and a stoichiometric amount of oxidant, in this case a peroxyacid (Scheme 5).<sup>8</sup> Starting with lactam **1a**, we used Ochiai's conditions but with methanol instead of water in order to form the stable carbamate **3a** and we were pleased to observe this product, albeit in low yield (5%), accompanied by starting material only.

Scheme 5. Ochiai's rearrangement of amide **19a** and our preliminary results for the ring contraction of **1a**

The acid presumably promotes the formation of a strongly electrophilic iodane like **25a-c** or perhaps even an iodonium ion **26** leading to the *N*-acylium ion **27** (Scheme 6). We tried the same conditions without the acid and no transformation was observed. Similarly, no reaction occurred in the absence of iodobenzene. Ochiai proposes that the acid is there to solubilize the iodosobenzene formed during the oxidation steps.<sup>9</sup> In our case, we replaced most of the water with methanol, so we cannot be certain of the structure of the  $\lambda^3$ -iodane formed.

Scheme 6. Possible formation of an iodonium ion **26**

Based on the premise that a more electrophilic iodane would lead to a faster rearrangement, we proceeded to fabricate a series of  $\lambda^3$ -iodanes and planned to use them stoichiometrically to increase our chances of success. The reaction conditions were otherwise the same as those described in Scheme 5 for compound **1a**. Table 1 shows a definite trend of increasing yield of product **3a** with increasing electrophilic character of the  $\lambda^3$ -iodane. The electron-rich *p*-methoxyphenyl iodide **28a** gave no trace of the desired product (entry 1) and already a simple ester at position 4 of the phenyl ring (**28c**) allowed for a 4-fold increase in yield as compared to the original experiment using phenyl iodide **28b** (compare entries 2 and 3). 4-Acetylphenyl iodide **28d** performed like its ester counterpart but 4-nitrophenyl iodide **28e** proved even better (entries 4 and 5, respectively). Strangely, changing to a 2-nitro group (**28f**), adding a second nitro group (**28g**), or using a perfluorinated iodoaryl (**28h**) decreased the yield of the product (entries 6, 7 and 8 respectively).

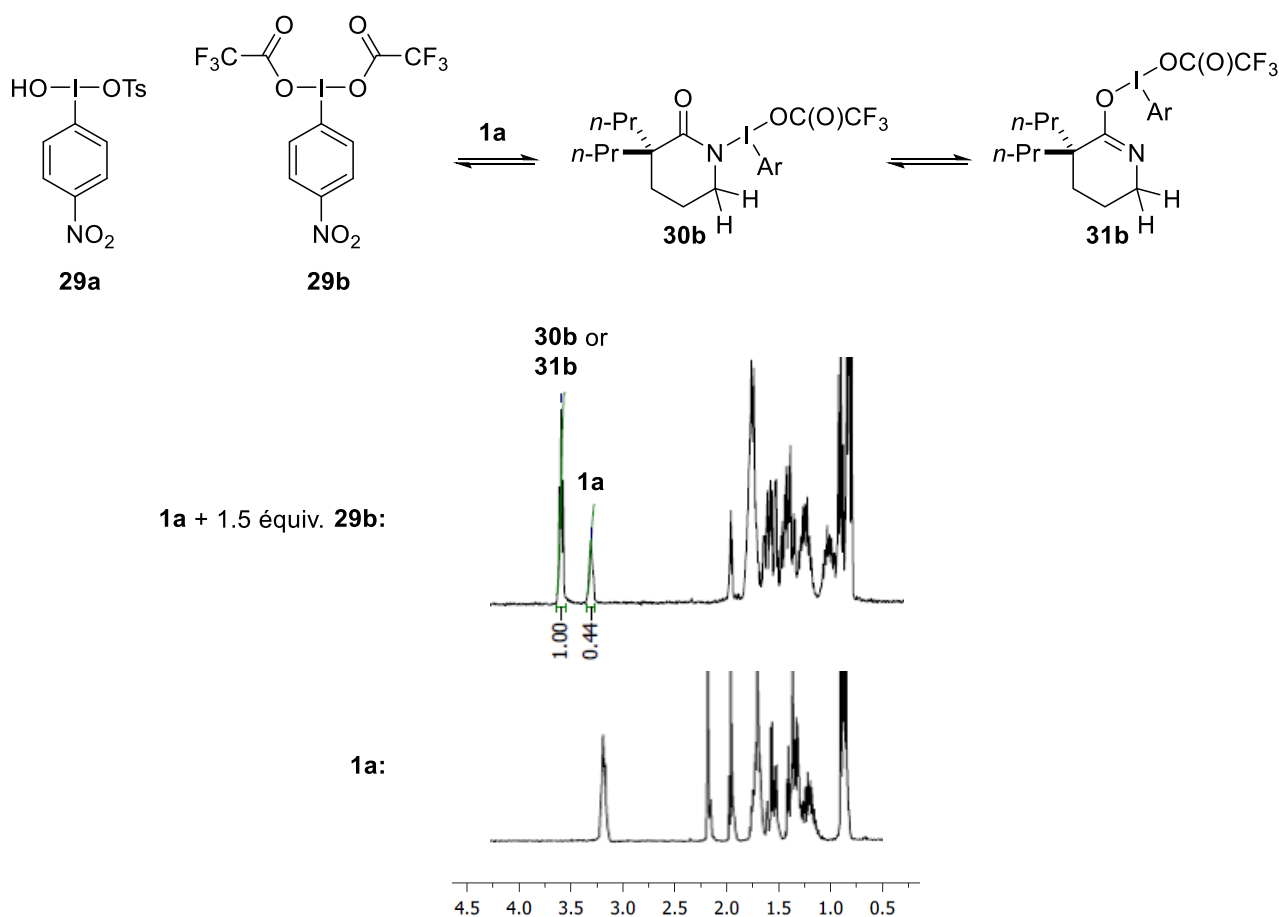
**Table 1.** Yield of carbamate **3a** as a function of the electrophilic character of  $\lambda^3$ -iodane reagent

Entry <sup>a</sup>	Iodide <b>28</b>	Yield <sup>b</sup> of <b>3a</b> (%)
1	4-(MeO)C <sub>6</sub> H <sub>4</sub> I <b>28a</b>	0
2	C <sub>6</sub> H <sub>5</sub> I <b>28b</b>	5 (10)
3	4-(MeOCO)C <sub>6</sub> H <sub>4</sub> I <b>28c</b>	23 (44)
4	4-(MeCO)C <sub>6</sub> H <sub>4</sub> I <b>28d</b>	~ 21
5	4-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> I <b>28e</b>	30 (56)
6	2-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> I <b>28f</b>	5 (17)
7	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> I <b>28g</b>	5 (17)
8	C <sub>6</sub> F <sub>5</sub> I <b>28h</b>	0

a) Conditions : Iodoarene (1 equiv.), *m*-CPBA (1.2 equiv.), aq HBF<sub>4</sub> (1.2 equiv.), MeCN : MeOH (9:1), 80 °C. b) Number in parentheses is the yield based on recovered starting material.

This may be indicative of the lower propensity of these electrophilic iodide species to be oxidized. Perhaps the *ortho* nitro group also provides steric hindrance. Based on the promising results obtained with 4-nitrophenyl iodide **28e**, we decided to further optimize the reaction conditions using this reagent.

We began by making and isolating  $\lambda^3$ -(*p*-nitrophenyl)iodane reagents and used them stoichiometrically, to insure that the incomplete *in situ* oxidation of the corresponding iodide was not causing the observed moderate yields. We prepared the *p*-nitro analog of Koser's reagent **29a** as well as the bis(trifluoroacetoxy)iodane **29b**, the *p*-nitro analog of PIFA (Scheme 7). We ran a series of NMR experiments mixing  $\lambda^3$ -iodane **29b** and lactam **1a** and found that a new set of signals appeared in deuterated chloroform. The new signals may correspond to complex **30b** or **31b**.



Scheme 7. Two  $\lambda^3$ -iodanes (**29a** and **29b**) used in the optimization of the ring-contraction reaction of lactam **1a** and partial NMR spectra ( $\text{CD}_3\text{CN}$ ) of **1a** and a mixture of **1a** and **29b**.

The signals for the free lactam **1a** and free  $\lambda^3$ -iodane **29b** were clearly visible also. We cannot be sure which of the complexes **30b** or **31b** is formed or if what we observe in the NMR spectrum is an average of the two complexes in equilibrium, but the new set of signals increased with increasing amount of **29b**.

in the mixture, up to a ratio of 3:1 in favor of the complex (**30b:1a** or **31b:1a**) when 2.5 equivalents of **29b** are added. Importantly, and unfortunately, we could observe the slow decomposition of reagent **29b** and the disappearance of the complex's signals with time. We ran the experiments again in deuterated acetonitrile and the decomposition was slower. However, the reactions are run at 80 °C and we can only assume that decomposition is faster at that temperature. Moreover, with time, while the aromatic signals belonging to free **29b** change and the new set of signals from the complex disappear, the signals belonging to lactam **1a** remain unaffected. It seemed, therefore, that the decomposition of the  $\lambda^3$ -iodane could be an issue.

$\lambda^3$ -Iodane **29a** gave slightly higher yields of carbamate **3a** (Table 2, entry 1) than when the combination of 4-nitrophenyl iodide/*m*-CPBA was used (Table 1, entry 5). We tested anhydrous acid to make sure that fortuitous hydrolysis of the reagent **29a** was not a problem and obtained a slight increase in yield (entry 2). A number of other Brønsted acids (*p*-TsOH•H<sub>2</sub>O, H<sub>2</sub>SO<sub>4</sub>, TFA) were tested but were less effective. Boron trifluoride etherate gave a result similar to HBF<sub>4</sub> (entry 3) but scandium triflate did not lead to a useful yield of **3a** (entry 4). It is likely that BF<sub>3</sub>•Et<sub>2</sub>O in the presence of methanol is a source of HBF<sub>3</sub>OMe,<sup>10</sup> explaining its similar efficiency to HBF<sub>4</sub>. Since BF<sub>3</sub>•Et<sub>2</sub>O is easier to handle and purify than HBF<sub>4</sub>, we continued with this additive switching now to  $\lambda^3$ -iodane **29b**. Under those conditions a moderate but encouraging 48% yield of **3a** was achieved (entry 5). In fact, the presence of the acidic additive was advantageous but no longer compulsory, as a 13% yield of **3a** was obtained without it (entry 6). Analysis of the NMR of the crude mixtures indicated that much decomposition of either iodane reagents occurred during the reaction.

**Table 2.** Yield of carbamate **3a** as a function reaction conditions using  $\lambda^3$ -iodanes **29a** or **29b**

Entry <sup>a</sup>	$\lambda^3$ -iodane	Acid	Yield <sup>b</sup> of <b>3a</b> (%)
1	<b>29a</b>	aq. HBF <sub>4</sub>	36 (60)
2	<b>29a</b>	HBF <sub>4</sub> /Et <sub>2</sub> O	40 (70)
3	<b>29a</b>	BF <sub>3</sub> •Et <sub>2</sub> O	36 (65)
4	<b>29a</b>	Sc(OTf) <sub>3</sub>	7 (34)
5	<b>29b</b>	BF <sub>3</sub> •Et <sub>2</sub> O	48 (73)
6	<b>29b</b> <sup>c</sup>	---	13 (40)
7	<b>29b</b> <sup>d</sup>	BF <sub>3</sub> •Et <sub>2</sub> O	72

a) Conditions: Iodane (1.05 equiv.), acid (1.2 equiv.), MeCN : MeOH (9:1), 80 °C. b) Number in parentheses is the yield based on recovered starting material. c) 2.1 equiv. d) 2.5 equiv.

We then increased the quantity of  $\lambda^3$ -iodane **29b** to 2.5 equivalents and obtained a 72% isolated yield of the carbamate **3a** (Table 2, entry 7). This yield can certainly be considered synthetically useful. Further increasing the amount of iodane did not improve the yield. A range of solvents was then tested (DCM,

PhMe, CHCl<sub>3</sub>, DCE, MeNO<sub>2</sub> et TFE, each in a 9:1 ratio with methanol). Only nitromethane was as good as acetonitrile but offered no advantage, so the latter was retained. Methanol as the solvent led to a drastic decrease in yield of product, presumably because it was oxidized by the iodane reagent. We found that the optimum temperature was 100 °C, which further increased the yield of **3a** to 77% as well as reducing the reaction time to 10 min (Table 3, entry 1). Under those conditions, we were able to decrease the amount of the BF<sub>3</sub>•Et<sub>2</sub>O required to a sub-stoichiometric level (30 mol%) without a detrimental effect on the yield of the rearranged product or on the reaction time. Lastly, we were able to lower the number of equivalents of λ<sup>3</sup>-iodane **29b** back down to 1.5 and those were the final conditions that gave constantly a 77-80% yield of carbamate **3a**.

It became apparent that the decomposition of the λ<sup>3</sup>-iodane reagent was going to limit the scope of this reaction as soon as we tried extending it to include less substituted lactams. Other α,α-disubstituted lactams rearranged in varying unoptimized yields (Table 3, yields are underestimated here for **3c,d** because of the volatility of the products). Except for **1b** and **1e** (entries 2 and 5), the conversions were complete as judged by NMR of the crude mixtures (Table 3, entries 1, 3, and 4). However, such was not the case for monosubstituted lactam **1f** (entry 6), which gave only traces of the desired product. The NMR of the crude mixture showed little conversion after 10 min. Unfortunately, it also showed extensive decomposition of the λ<sup>3</sup>-iodane **29b** after 15 min. Adding more reagent was not an option because of the slow rate of rearrangement and the fast rate of decomposition. A sturdier reagent was needed, and that new reagent had to remain electrophilic enough to promote the rearrangement.

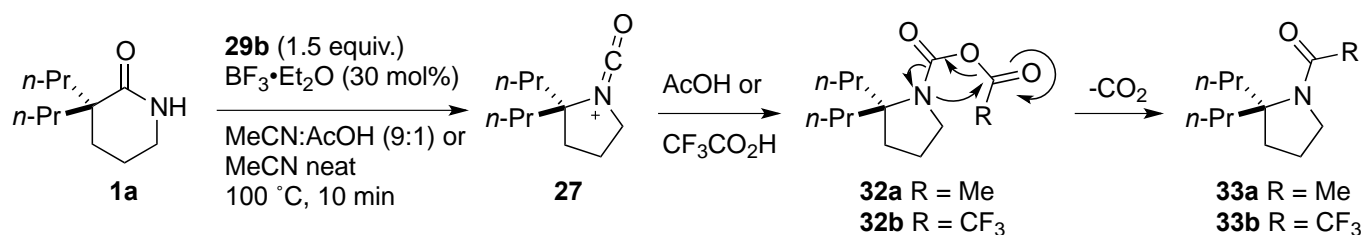
**Table 3.** Ring contraction of lactams **1a-f**

Entry	lactam	R <sup>1</sup>	R <sup>2</sup>	Conversion <sup>a</sup> (%)	Isolated yield of <b>3</b> (%)
1	<b>1a</b>	<i>n</i> -Pr	<i>n</i> -Pr	100	77 <sup>b</sup>
2	<b>1b</b>	Bn	Bn	29	20
3	<b>1c</b>	<i>n</i> -Pr	Me	100	54 <sup>c</sup>
4	<b>1d</b>	Me	Me	100	<10 <sup>c</sup>
5	<b>1e</b>	-(CH <sub>2</sub> ) <sub>4</sub> -		46	24
6	<b>1f</b>	<i>n</i> -Pr	H	trace	trace

a) Determined by NMR. b) Fully optimized isolated yield as described. c) Clean crude reaction mixtures; the low yields are due to the volatility of the products.

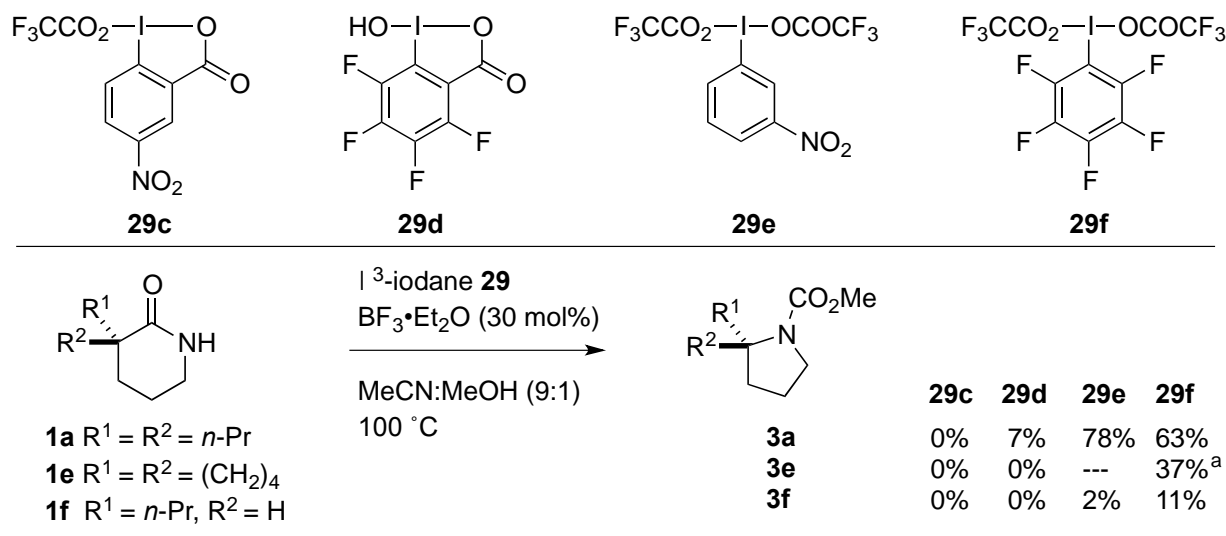
We checked if the decomposition of the iodane might be due in part to the oxidation of methanol present in the mixture. Replacing the latter with other additives led to a decrease in yield and no sign of

amelioration of the decomposition rate of the iodane. We tried acetonitrile with *t*-butanol, acetic acid, or water, or just acetonitrile, but to no avail. We have noticed the formation of small amounts of compounds **33a** (4%) and **33b** (37%) when replacing methanol with acetic acid or simply removing methanol, respectively. We believe the compounds are made from the attack of acetic acid or trifluoroacetic acid on the *N*-acylium ion **27** and loss of carbon dioxide as shown in Scheme 8.



Scheme 8. Plausible formation products **33a** and **33b**

We were left with no choice but to discover a reactive  $\lambda^3$ -iodane reagent that did not decompose so fast or that was much more reactive so as to promote a faster rearrangement. First, TMSOTf was added to the optimized reaction conditions, thus replacing the trifluoroacetate ligands by trifluoromethanesulfonate ones. With these new conditions, carbamate **3a** was isolated in only 43% yield (not shown). We then elected to prepare *de novo*  $\lambda^3$ -iodane reagents **29c-f** in the hope of striking the right balance between reactivity and stability.  $\lambda^3$ -Iodanes **29c** and **29d** proved more stable and degraded more slowly than **29b** but were not reactive enough (Scheme 9). The internal ligand may confer a higher stability to those two reagents but also a lesser degree of electrophilicity or perhaps prevent the formation of an iodonium ion, whichever the case may be (c.f. Scheme 6). The (*m*-nitrophenyl)iodane **29e** was marginally better than its *p*-nitro analogue **29b**. However,  $\lambda^3$ -iodane **29f** showed a markedly better performance with lactams **1e** and **1f**. Because the yield of carbamate **3a** was not higher using iodane **29f** than using iodane **29b** or **29e**, we think that their reactivities are similar. However, iodane **29f** is sufficiently more stable such that reaction times can be prolonged (up to 24 h) resulting in more conversion of the starting material. Its structure having no proton, the fate of iodane **29f** is difficult to assess by spectroscopy. Though not yet at the level we would like it to be, iodane **29f** is a hopeful lead to a better performing promotor and reaction conditions.



a) 72% conversion by NMR after 24 h.

Scheme 9. Ring-contraction of lactams **1a, e, f** using  $\lambda^3$ -iodane **29c-f**

Our efforts to promote the direct ring-contraction of less substituted lactams are continuing and new  $\lambda^3$ -iodanes are being prepared.  $\alpha, \alpha$ -Disubstituted lactams rearrange well but the design of novel  $\lambda^3$ -iodane reagents will be required to increase the scope of the reaction for less substituted lactams. Ideally, we would like to find conditions that require only a catalytic amount of the iodide and *in situ* oxidation, but first we need to confer to the reagent a high reactivity and adequate stability, which can be a contradiction in terms! Different and original  $\lambda^3$ -iodanes will be required.

## EXPERIMENTAL

Unless otherwise noted all reactions were performed under an argon atmosphere. Solvents were distilled from potassium/benzophenone ketyl (THF, toluene) or from calcium hydride ( $\text{CH}_2\text{Cl}_2$ , MeCN), or dried with  $\text{CaSO}_4$ , then fractionally distilled (MeOH). Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on a 300 MHz or 400 MHz spectrometer. Carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were recorded on a 75.5 MHz or 100.7 MHz spectrometer. NMR samples were dissolved in chloroform-*d* and chemical shifts are reported in ppm ( $\delta$  units) relative to the residual undeuterated solvent. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet. High-resolution mass spectrometry was performed by electrospray time-of-flight. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel coated glass plate visualized under UV (254 nm) and TLC stains such as vanillin,  $\text{KMnO}_4$ , PMA, ninhydrin, or by  $^1\text{H}$  NMR analysis. Silica gel (230-400 mesh) was used for flash chromatography.

### General procedure for the bis-alkylation of lactams

To a 0.5 M solution of LiHMDS (2.75 equiv) cooled to  $-78\text{ }^{\circ}\text{C}$  was added dropwise a 0.75 M solution of protected lactam in THF. This solution was stirred for 1 h while slowly warming to rt, then cooled back down to  $-78\text{ }^{\circ}\text{C}$ . Alkyl halide (5.00 equiv) was then added dropwise and the solution was left to stir while warming up slowly to rt until completion. A saturated aqueous solution of  $\text{NH}_4\text{Cl}$  was added to the reaction mixture, then the THF was removed under reduced pressure. The resulting suspension was diluted in more water, then extracted with EtOAc three times. The organic layers were combined, dried with anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure.

### General procedure for the deprotection of the Boc group

Boc-protected compound was dissolved in DCM (0.6 M). Then was added an equal volume of TFA dropwise. The solution was stirred at rt until completion, then it was diluted with toluene and evaporated under reduced pressure. To the residue was added NaOH (1 N, 10 mL), and that solution was then extracted with  $\text{Et}_2\text{O}$  five times, then the organic layers were combined, dried over anhydrous  $\text{MgSO}_4$ , filtered and evaporated.

### General procedure for Iodine(III)-promoted lactam rearrangement

In an oven dried sealable flask, the lactam was dissolved in a mixture of MeCN and MeOH (9:1; 0.1 M).  $4\text{-NO}_2\text{C}_6\text{H}_4\text{I}(\text{OCOCF}_3)_2$  (**29b**) (1.50 equiv) and  $\text{BF}_3\cdot\text{OEt}_2$  (30 mol%) were added to the mixture, then the flask was sealed and heated to  $100\text{ }^{\circ}\text{C}$  (bath temperature). After the reaction was complete as shown by NMR monitoring, the mixture was cooled back down to rt, quenched by successive addition of a saturated aqueous solution of  $\text{NaHCO}_3$  and 10% aqueous  $\text{Na}_2\text{S}_2\text{O}_3$ , then the aqueous layer was extracted three times with EtOAc. The organics were combined, dried with anhydrous  $\text{MgSO}_4$ , filtered and concentrated in vacuo.

### 3,3-Dipropylpiperidin-2-one (1a)

Prepared from valerolactone according to known procedures.<sup>11</sup>

### 3,3-Dibenzylpiperidin-2-one (1b)

*t*-Butyl 2-oxopiperidine-1-carboxylate<sup>11</sup> was treated according to the general procedure for the bis-alkylation of lactams using benzyl bromide as the alkyl halide on a 2.51 mmol scale with a reaction time of 18 h. The crude material was purified by flash chromatography (5%, then 10% EtOAc/Hex) to yield *t*-butyl 3,3-dibenzyl-2-oxopiperidine-1-carboxylate (**34**) (81%) as a white solid.

**mp:** 84-88 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.26-7.17 (m, 10H), 3.39 (d, 2H, *J* = 13.2 Hz), 3.18 (t, 2H, *J* = 5.9 Hz), 2.64 (d, 2H, *J* = 13.2 Hz), 1.74-1.70 (m, 2H), 1.54 (s, 9H), 1.40-1.32 (m, 2H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 176.1 (s), 153.2 (s), 137.5 (s), 130.9 (d), 128.2 (d), 126.8 (d), 82.7 (s), 51.2 (s), 47.2 (t), 46.1 (t), 28.4 (t), 28.2 (q), 20.1 (t). **IR** (neat) ν (cm<sup>-1</sup>) 3031, 2985, 1713, 1685, 1495. **HRMS** calculated for [C<sub>24</sub>H<sub>29</sub>NO<sub>3</sub>+Na]<sup>+</sup>: 402.2040, found: 402.2034.

*t*-Butyl 3,3-dibenzyl-2-oxopiperidine-1-carboxylate (**34**) was treated according to the Boc deprotection general procedure on a 1.92 mmol scale with a reaction time of 5 min. The crude material was purified by flash chromatography (5% MeOH/DCM) to yield title compound **1b** (88%) as a white solid.

**mp:** 132-136 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) 7.31-7.18 (m, 10H), 6.04 (br. s, 1H), 3.41 (d, 2H, *J* = 13.1 Hz), 2.87 (td, 2H, *J* = 5.8, 2.5 Hz), 2.61 (d, 2H, 13.1 Hz), 1.71-1.67 (m, 2H), 1.38-1.30 (m, 2H). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 175.9 (s), 138.0 (s), 130.9 (d), 128.2 (d), 126.6 (d), 48.0(s), 45.2 (t), 42.7 (t), 27.7 (t), 20.0 (t). **IR** (neat) ν (cm<sup>-1</sup>) 3195, 3028, 2936, 1647, 1454. **HRMS** calculated for [C<sub>19</sub>H<sub>21</sub>NO+Na]<sup>+</sup>: 302.1515, found: 302.1515.

### 3-Methyl-3-propylpiperidin-2-one (**1c**)

*t*-Butyl 3-allyl-2-oxopiperidine-1-carboxylate<sup>12</sup> (**35**) (462 mg, 1.93 mmol) was dissolved in THF (21 mL) and cooled to -78 °C. A 1 M solution of LiHMDS in THF (2.12 mL, 2.12 mmol) was added, and the mixture was stirred for 1 h. Then, MeI (0.36 mL, 5.79 mmol) was added and the solution was allowed to warm up to rt and stirred for 18 h. Saturated aqueous NH<sub>4</sub>Cl (25 mL) was added and the aqueous layer was extracted with DCM (3 × 25 mL). The organic layers were combined, dried with anhydrous MgSO<sub>4</sub>, filtered and evaporated *in vacuo*. The crude mixture was purified by column chromatography (7% EtOAc/Hex) to afford 322 mg (66%) of *t*-butyl 3-allyl-3-methyl-2-oxopiperidine-1-carboxylate (**36**) as colorless oil. Characterization matches the data previously reported in the literature.<sup>13</sup>

A solution of *t*-butyl 3-allyl-3-methyl-2-oxopiperidine-1-carboxylate (**36**) (267 mg, 1.05 mmol) in EtOAc (0.1 M) was purged with argon for a few minutes. A catalytic amount of Pd/C (10%) was then added and H<sub>2</sub> was bubbled through the reaction mixture for several seconds. The solution was stirred under an atmosphere of H<sub>2</sub> for 45 min, then was purged with argon again for several minutes, filtered over Celite® and concentrated under reduced pressure. *t*-Butyl 3-methyl-2-oxo-3-propylpiperidine-1-carboxylate (**37**) was obtained (255 mg, 95%) as a colorless oil and was used without further purification.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.69-3.50 (m, 2H), 1.92-1.73 (m, 3H), 1.70-1.45 (m, 3H), 1.50 (s, 9H), 1.37-1.24 (m, 2H), 1.20 (s, 3H), 0.90 (t, 3H, *J* = 7.2 Hz). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 177.9 (s), 154.0 (s), 82.5 (s), 47.6 (t), 44.8 (s), 42.5 (t), 33.7 (t), 28.2 (q), 25.7(q), 20.0 (t), 17.4 (t), 14.7

(q). **IR** (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 2958, 1710, 1250, 1143. **HRMS** calculated for  $[\text{C}_{14}\text{H}_{25}\text{NO}_3+\text{Na}]^+$ : 278.1727, found: 278.1717.

*t*-Butyl 3-methyl-2-oxo-3-propylpiperidine-1-carboxylate (**37**) was treated according to the general procedure for Boc deprotection on a 1.09 mmol scale with a reaction time of 5 min. The title compound **1c** was obtained (97%) as a white solid and was used without further purification.

**mp**: 47-49 °C. **<sup>1</sup>H NMR** (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 5.82 (br. s, 1H), 3.29-3.24 (m, 2H), 1.85-1.75 (m, 3H), 1.67 (ddd, 1H,  $J = 13.1$  Hz, 12.1 Hz, 4.7 Hz), 1.60-1.21 (m, 4H), 1.19 (s, 3H), 0.90 (t, 3H,  $J = 7.2$  Hz). **<sup>13</sup>C NMR** (75.5 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm) 178.2 (s), 43.0 (t), 42.1 (t), 41.5 (s), 32.7 (t), 25.9 (q), 19.7 (t), 17.5 (t), 14.8 (q). **IR** (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3179, 2930, 1644, 1415. **HRMS** calculated for  $[\text{C}_9\text{H}_{17}\text{NO}+\text{Na}]^+$ : 178.1202, found: 178.1203.

### 3,3-Dimethylpiperidin-2-one (**1d**)

*t*-Butyl 2-oxopiperidine-1-carboxylate<sup>11</sup> was treated according to the general procedure for the bis-alkylation of lactams using methyl iodide as the alkyl halide on a 2.51 mmol scale with a reaction time of 18 h. The crude material was purified by flash chromatography (8%, then 20% EtOAc/Hex) to yield *t*-butyl 3,3-dimethyl-2-oxopiperidine-1-carboxylate (**38**) (46%) as colorless oil along with the mono-alkylated compound **39**<sup>12</sup> (32%), also as colorless oil.

*t*-Butyl 3,3-dimethyl-2-oxopiperidine-1-carboxylate (**38**) was treated according to the general procedure for the deprotection of the Boc group on a 1.00 mmol scale with a reaction time of 10 min. The crude material was purified by flash chromatography (100% DCM, then 5% MeOH/DCM) to yield title compound (57%) as a white solid. Characterization matches the data previously reported in the literature.<sup>14</sup>

### 7-Azaspiro[4.5]decan-6-one (**1e**)

Prepared from valerolactone according to known procedures.<sup>11</sup>

### 3-Propylpiperidin-2-one (**1f**)

Prepared from valerolactone according to known procedures.<sup>11</sup>

### Methyl 2,2-dipropylpyrrolidine-1-carboxylate (**3a**)

Synthesized from **1a** according to a slightly modified version of the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.27 mmol scale with a reaction time of 10 min. The procedure was modified as follows: 1.75 equivalents of the iodane were used instead of 1.50 equivalents.

The crude material was purified by flash chromatography (2%, then 10% EtOAc/Hex) to yield title compound (81%) as a colorless oil. Characterization matches the data previously reported in the literature.<sup>1d</sup>

### Methyl 2,2-dibenzylpyrrolidine-1-carboxylate (3b)

Synthesized from **1b** according to the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.18 mmol scale with a reaction time of 24 h. The crude material was purified by flash chromatography (2%, then 5%, then 75% EtOAc/Hex) to yield title compound (20%) as a white solid.

**mp:** 35-36 °C. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) **Rotamer A:** 7.07-7.31 (m, 10H), 3.91 (s, 3H), 3.52 (d, 2H, *J* = 13.4 Hz), 3.00 (t, 2H, *J* = 7.1), 2.74 (d, 2H, *J* = 13.4), 1.91 (t, 2H, *J* = 7.1), 0.85 (quint, 2H, *J* = 7.1 Hz). **Rotamer B:** 7.07-7.31 (m, 10H), 3.82 (s, 3H), 3.71 (d, 2H, *J* = 13.2 Hz), 2.88 (t, 2H, *J* = 7.1), 2.74 (d, 2H, *J* = 13.2), 1.87 (t, 2H, *J* = 7.1), 0.86 (quint, 2H, *J* = 7.1 Hz). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) **Rotamer A:** 155.6 (s), 138.0 (s), 130.6 (d), 128.4 (d), 126.6 (d), 66.9 (s), 52.4 (q), 49.7 (t), 44.4 (t), 34.5 (t), 21.2 (t). **Rotamer B:** 155.0 (s), 138.5 (s), 130.8 (d), 128.2 (d), 126.4 (d), 67.6 (s), 52.3 (q), 48.6 (t), 42.9 (t), 33.3 (t), 21.7 (t). **IR** (neat) ν (cm<sup>-1</sup>) 3029, 2956, 1687, 1446, 1373. **HRMS** calculated for [C<sub>20</sub>H<sub>23</sub>NO<sub>2</sub>+Na]<sup>+</sup>: 332.1621, found: 332.1617.

### Methyl 2-methyl-2-propylpyrrolidine-1-carboxylate (3c)

Synthesized from **1c** according to the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.32 mmol scale with a reaction time of 4.5 h. The crude material was purified by flash chromatography (2%, then 10% EtOAc/Hex) to yield title compound (54%) as a colorless oil.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) **Rotamer A:** 3.65 (s, 3H), 3.55-3.48 (m, 2H), 1.92 (ddd, 1H, *J* = 11.5 Hz, 7.5 Hz, 7.5 Hz), 1.59-1.84 (m, 5H), 1.34-1.09 (m, 2H), 1.31 (s, 3H), 0.90 (t, 3H, *J* = 7.25 Hz). **Rotamer B:** 3.65 (s, 3H), 3.33 (ddd, 2H, *J* = 10.8 Hz, 7.4 Hz, 7.4 Hz), 1.92 (ddd, 1H, *J* = 11.5 Hz, 7.5 Hz, 7.5 Hz), 1.59-1.84 (m, 5H), 1.34-1.09 (m, 2H), 1.31 (s, 3H), 0.90 (t, 3H, *J* = 7.25 Hz). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 154.9 (s), 63.3 (s), 51.8 (q), 48.4 (t), 41.0 (t), 38.5 (t), 25.0 (q), 22.3 (t), 18.0 (t), 14.7 (q). **IR** (neat) ν (cm<sup>-1</sup>) 2960, 1694, 1442, 1370, 1098. **HRMS** calculated for [C<sub>10</sub>H<sub>19</sub>NO<sub>2</sub>+Na]<sup>+</sup>: 208.1308, found: 208.1307.

### Methyl 2-dimethylpyrrolidine-1-carboxylate (3d)

Synthesized from **1d** according to the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.32 mmol scale with a reaction time of 4.5 h. The conversion was followed by NMR

but it was extremely difficult to purify this compound and separate it from solvent due to its volatility. NMR contains Et<sub>2</sub>O and EtOAc but the signals of **3d** are clear and no SM (**1d**) remains.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) as a mixture of two rotamers: 3.65 (s, 3H), 1.78-1.47 (m, 4H), 1.36 (bs, 6H).

#### **Methyl 1-azaspiro[4.4]nonane-1-carboxylate (3e)**

Synthesized from **1e** according to a slightly modified version of the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.33 mmol scale with a reaction time of 24 h. The procedure was modified as follows: iodane **29f** was used instead of the usual **29b**. The crude material was purified by flash chromatography (3% EtOAc/Hex) to yield title compound (35%) as a colorless oil. Characterization matches the data previously reported in the literature.<sup>14</sup>

#### **Methyl 2-propylpyrrolidine-1-carboxylate (3f)**

Synthesized from **1f** according to a slightly modified version of the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.35 mmol scale with a reaction time of 24 h. The procedure was modified as follows: iodane **29f** was used instead of the usual **29b**. The crude material was purified by flash chromatography (2%, then 15% EtOAc/Hex) to yield title compound (11%) as a colorless oil. Characterization matches the data previously reported in the literature.<sup>14</sup>

#### **1-[Hydroxy(tosyloxy)iodo]-4-nitrobenzene (29a)**

Synthesized according to a known literature procedure.<sup>15</sup> Characterization matched the data previously reported in the literature.<sup>16</sup>

#### **1-[Bis(trifluoroacetoxy)iodo]-4-nitrobenzene (29b)**

Synthesized according to a known literature procedure.<sup>17</sup> Characterization matches the reported data.

#### **1-Trifluoroacetoxy-5-nitro-1,2-benziodoxole-3(1H)-one (29c)**

Synthesized according to a slight modification of two previously reported procedures.<sup>18</sup> Neat 2-iodobenzoic acid (3.00 g, 12.1 mmol) was cooled down to 0 °C, to which was added a mixture of fuming HNO<sub>3</sub> (3.0 mL) and concentrated H<sub>2</sub>SO<sub>4</sub> (13.5 mL). This mixture was then stirred at 0 °C for 1 h, then at rt for 30 min, and finally at 135 °C for 2 h, before being cooled back down to rt. The resulting solution was poured into plenty of ice water and filtered. The solid was transferred to an Erlenmeyer flask and suspended in water (300 mL), then heated to a boil. A solution of KI (2.41 g, 14.5 mmol) in water (15 mL) acidified to pH 3 with a few drops of concentrated H<sub>2</sub>SO<sub>4</sub> was added portion-wise to this boiling

suspension (I<sub>2</sub> vapors were generated with each portion). Omitting this step as in Subramanian's report yields the iodoso analog. The solution was filtered while still boiling, then the filtrate was stored at 4 °C for 18 h after which time the desired compound precipitated. 2-Iodo-5-nitrobenzoic acid was then collected by filtration while still cold to afford 1.73 g (49%) as a 13:2 mixture with the undesired 2-iodo-3-nitrobenzoic acid isomer. The inseparable mixture was used as is in the next step. Characterization matches the data previously reported in the literature.<sup>18b</sup>

2-Iodo-5-nitrobenzoic acid (750 mg, 2.56 mmol) was dissolved in a mixture of CHCl<sub>3</sub> (2.6 mL) and TFA (7.7 mL). Oxone<sup>®</sup> (1.38 g, 4.48 mmol, 1.75 equiv) was added, then the mixture was protected from light and stirred at rt for 40 h. The solvent was evaporated under reduced pressure and the resulting solid was repeatedly triturated with CHCl<sub>3</sub> and filtered. The filtrate was concentrated under reduced pressure to give 424 mg (41%) of the desired iodane **29c**.

**mp:** 178 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ (ppm) 9.07 (d, 1H, *J* = 2.6 Hz), 8.85 (dd, 1H, *J* = 9.0, 2.6 Hz), 8.25 (d, 1H, *J* = 9.0 Hz). **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>, using trifluorotoluene as reference) δ (ppm) -74.3 (s). **IR** (neat) ν (cm<sup>-1</sup>) 3091, 1605, 1520, 1158, 818. A <sup>13</sup>C NMR spectrum could not be acquired due to solubility and solvent incompatibility issues. A mass spectrum could not be acquired because of the instability of this compound, even under mild ionization conditions.

#### 1-Hydroxy-4,5,6,7-tetrafluoro-1,2-benziodoxole-3(1*H*)-one (**29d**)

Synthesized according to a known literature procedure.<sup>19</sup> Characterization matches the reported data.

#### 1-[Bis(trifluoroacetoxy)iodo]-4-nitrobenzene (**29e**)

Synthesized according to a known literature procedure.<sup>17</sup> Characterization matches the reported data.

#### 1-(2,2-Dipropylpyrrolidin-1-yl)ethanone (**33a**)

Synthesized from **1a** according to a slightly modified version of the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.27 mmol scale with a reaction time of 24 h. The procedure was modified as follows: AcOH was used instead of MeOH in an equal volume. Once the heating was stopped, the mixture was diluted with 10 mL of MeOH and 1 mL of Et<sub>3</sub>N and the solution was stirred at rt for 18 h. The crude material was purified by flash chromatography (5%, then 50% EtOAc/Hex) to yield title compound (4%) as a colorless film.

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.44-3.40 (m, 2H), 2.09-1.96 (m, 2H), 2.02 (s, 3H), 1.85-1.77 (m, 3H), 1.67-1.57 (m, 3H), 1.34-1.04 (m, 4H), 0.89 (t, 6H, *J* = 7.2 Hz). **<sup>13</sup>C NMR** (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 168.8 (s), 68.0 (s), 50.7 (t), 39.9 (t), 35.0 (t), 24.8 (t), 23.2 (q), 17.9 (t), 14.7 (q). **HRMS** calculated for [C<sub>12</sub>H<sub>23</sub>NO+Na]<sup>+</sup>: 220.1672, found: 220.1677.

**1-(2,2-Dipropylpyrrolidin-1-yl)-2,2,2-trifluoroethanone (33b)**

Synthesized from **1a** according to a slightly modified version of the general procedure for the iodine(III)-promoted lactam rearrangement on a 0.27 mmol scale with a reaction time of 24 h. The procedure was modified as follows: no MeOH was used and more MeCN was added to replace it. Once the heating was stopped, the mixture was diluted with 10 mL of MeOH and 1 mL of Et<sub>3</sub>N and the solution was stirred at rt for 18 h. The crude material was purified by flash chromatography (2% EtOAc/Hex) to yield title compound (30%) as an inseparable mixture with 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>I in a 3.2:1 mixture of iodoaryl to title material by NMR integration. The yield given was corrected to account for this impurity and the compound was characterized as a mixture.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm) 3.62 (t, 2H, *J* = 6.3 Hz), 2.03 (ddd, 2H, *J* = 13.0, 13.0, 4.3 Hz), 1.90-1.84 (m, 4H), 1.65 (ddd, 2H, *J* = 13.0, 13.0, 4.3 Hz), 1.37-1.21 (m, 2H), 1.18-1.03 (m, 2H), 0.89 (t, 6H, *J* = 7.2 Hz). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ (ppm) 70.8 (s), 49.0 (t; *J*<sub>C-F</sub> = 3.9 Hz (q)), 39.0 (t), 34.3 (t), 23.9 (t), 17.6 (t), 14.5 (q). (Note : Even after prolonged acquisition, the two carbons of the trifluoroethanone fragment did not appear, presumably due to long relaxation time and to the splitting due to coupling with fluorine reducing the overall signal-to-noise ratio.) <sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>) δ (ppm) -72.5 (s). HRMS calculated for [C<sub>12</sub>H<sub>20</sub>F<sub>3</sub>NO+Na]<sup>+</sup>: 274.1389, found: 274.1397.

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