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Nitrite-Catalyzed Stereoselective Bromocyclization to Access Tetrahydrofuran Scaffolds under Batch and Flow: An Economic and Sustainable Approach to Gram-Scale Total Synthesis of Posaconazole

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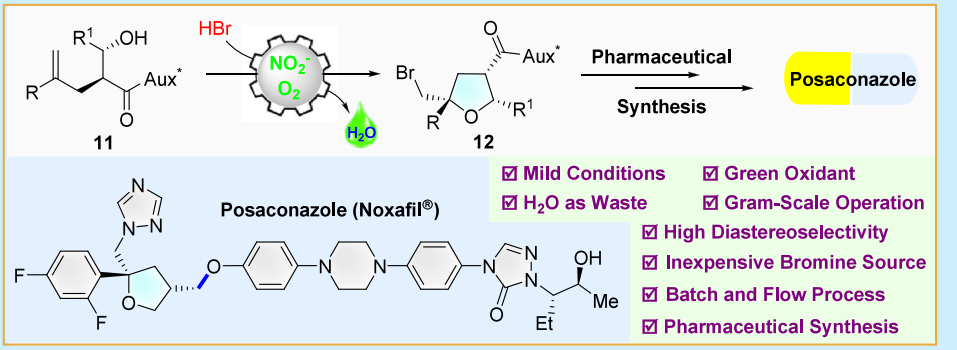

ABSTRACT: A highly efficient and concise bromocyclization has been successfully achieved, in which chiral auxiliary-substituted 4-en-1-ol derivatives can be transformed to valuable THF scaffolds in an economic and green manner. Production was successfully scaled up under both batch and continuous flow processes. A distinctive feature of our synthetic approach is that water constitutes the primary byproduct. Notably, gram-scale total synthesis of posaconazole was successfully achieved, underscoring the industrial applicability and cost-effectiveness of this transformation.

Posaconazole (Noxafil) is a second-generation triazole antifungal drug derived from the scaffold of itraconazole.[1] This drug, similar to itraconazole in its mechanism of action, blocks the enzyme lanosterol 14α-demethylase, thereby inhibiting the formation of ergosterol—a critical sterol component of fungal cell membranes. This destruction compromises the integrity and function of the membrane in fungal pathogens. The alteration of fungal cell membrane properties and physiological contributions caused by the accumulation of 14α-methyl sterol precursors impedes cellular growth and division, thereby exerting an antifungal effect.[2] Notably, posaconazole is a versatile and significant antifungal medication that is effective against numerous fungal species, involving common pathogens such as Aspergillus species and Candida species, as well as new pathogens such as Fusarium species, *Cryptococcus neoformans*, and Zygomycetes species.[3] Therefore, the development of highly efficient strategies to access this pharmaceutical is a paramount objective.

The conventional and industrialized synthesis routes for posaconazole involved constructing the key structures of **1** and **2** (Figure 1A). The scaffold **2** could be facilely obtained from L-lactic acid and the related substrates.[4] There were more challenges in the construction of tetrahydrofuran (THF) scaffold **1** due to its distinctive architecture featuring 1,3-nonadjacent stereocenters and a tetrasubstituted carbon stereocenter. Iodocyclization was well established as the industrial process to form the vital intermediate from a chiral alcohol **3** or **5** and expensive iodine (Figure 1B-i and 1B-ii).[5a−d] The chiral alcohol **3** bearing ether or ester as the protecting group reacted with excess amount of iodine to give the desired product **4** in high yield with moderate enantioselectivity (Figure 1B-i).[5a−c] The iodocyclization of a chiral auxiliary-modified alcohol **5** and iodine represented a pivotal synthetic approach to construct the key entity **6** with moderate *dr* value (Figure 1B-ii).[5a,d] Another type of method was utilizing the complicated compound **7** to generate the

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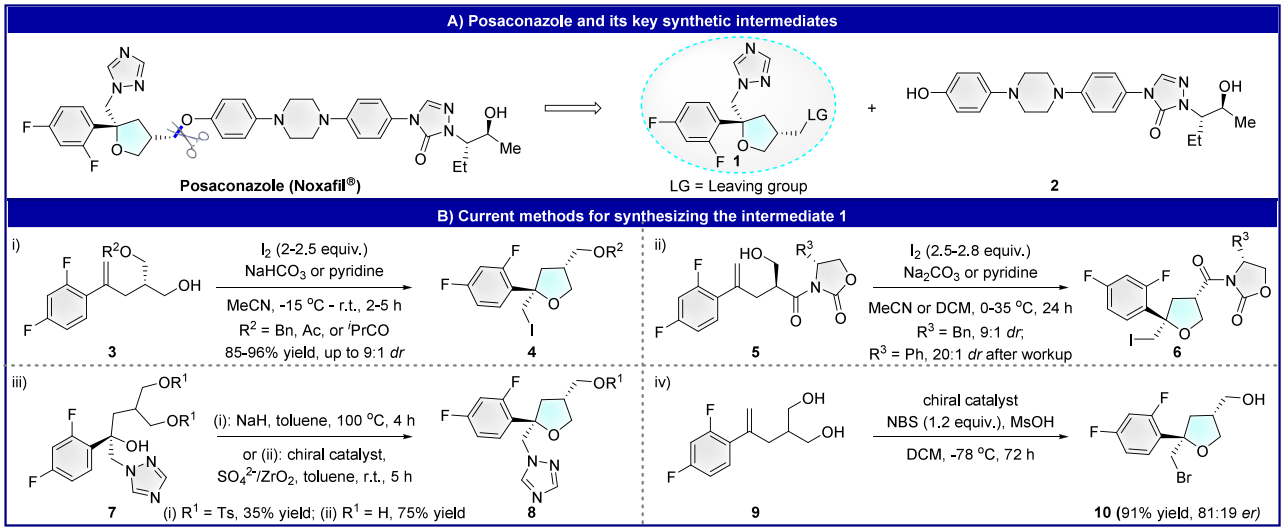
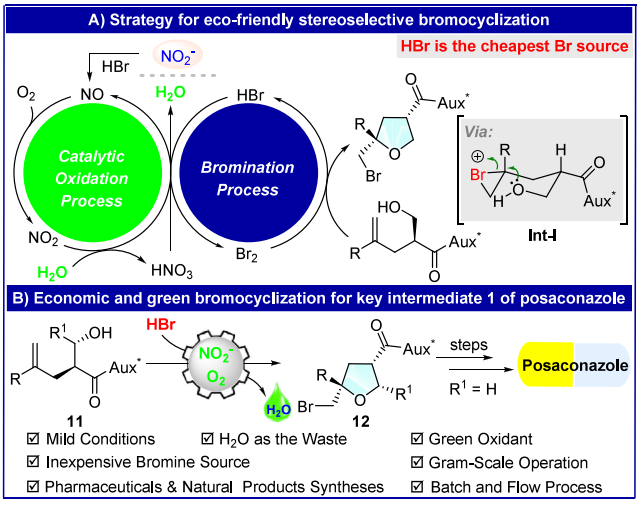


Figure 1. Posaconazole, its key synthetic intermediates, and the synthetic strategies for structure **1**.

tetrahydrofuran unit **8** via S_N2 or S_N1 substitution, resulting in extended processes for the synthesis of posaconazole (Figure 1B-iii).[6] A novel organosulfide-catalyzed asymmetric bromocyclization was applied to form the product **10** with moderate enantioselectivity from a diol substrate **9** and NBS, which provided an innovative approach to the formal synthesis of posaconazole (Figure 1B-iv).[7] Among them, structures **4**, **6**, **8**, and **10** could be easily transformed to intermediate **1**. Moreover, a substituted chiral 2,5-dihydrofuran scaffold obtained from olefin metathesis could be utilized for the formal synthesis of posaconazole.[8] Though numerous methods have been applied to fabricate this key unit in high-efficiency, the development of more concise, efficient, inexpensive, environmentally benign, and gentle procedures for achieving this exquisite entity, which holds promise for industrial application, remains a highly sought-after and coveted goal.

Considering the cost economy, environmental economy, and atom economy, bromocyclization is the better strategy to access the key intermediate **1** via alkyne addition reaction.[9] Notably, bromocyclization strategies have been widely employed in the formation of significant scaffolds[9a−k], and their application extends to the construction of natural products and pharmaceuticals[9i−k]. Although various bromide reagents are available, hydrobromic acid (HBr) stands out as the most economical and abundant source of bromine, effectively serving as a potent electrophilic bromine reagent.[10] Theoretically, Br_2 can be generated from HBr under the oxygen atmosphere along with water as the single byproduct;[11] however, a relatively slow reaction rate can be attributed to an activation barrier of 14 kJ mol^{-1}.[12] Recently, our research efforts have concentrated on the realms of halogen catalysis and transformation.[13] Notably, we have facilely accomplished the nitrite-catalyzed bromocyclization of tryptamines/tryptophols[13b] with HBr as the bromine source under air atmosphere, in which the nitrite salt serves as a matching medium to bridge the gap between O_2 activation and HBr reoxidation. Hence, we considered that nitrite-catalyzed stereoselective bromocyclization would be a concise, inexpensive, efficient, and green route to access tetrahydrofuran scaffolds via chiral auxiliary strategy (Scheme 1A). Mechanistically, the readily available nitrite salt possesses a distinctive redox property, enabling it to release nitric oxide (NO) under

Scheme 1. Economic, Green, and Enantioselective Bromocyclization to Access Tetrahydrofuran Scaffolds



acidic conditions.[14a−f] The NO formed *in situ* can be oxidized by oxygen to produce nitrogen dioxide (NO_2), which controllably reoxidizes HBr to Br_2. Additionally, HNO_3 generated by dissolving NO_2 in water has the capability to oxidize HBr to Br_2 as well. Therefore, the nitrite-catalyzed oxidation can achieve an appropriate rate to release Br_2, leading to access to a mild bromocyclization reaction and forming water as byproduct. Notably, the stereoselectivity of this transformation is determined by chair-conformation intermediate **Int-I**. Herein, we have approached a nitrite-catalyzed economic and green enantioselective bromocyclization of substituted 4-en-1-ol derivates to facilely access valuable chiral tetrahydrofuran units with high diastereoselectivity via a chiral auxiliary strategy in both batch and flow modes (Scheme 1B). Notably, a gram-scale synthesis of posaconazole has been successfully accomplished.

We initiated our optimization process by conducting a stereoselective bromocyclization of substrate **11a**, resulting in the formation of the substituted THF **12a**. This reaction was carried out in the presence of HBr as the bromine source, $NaNO_2$ as the catalyst, O_2 as the oxidant, and acetonitrile as

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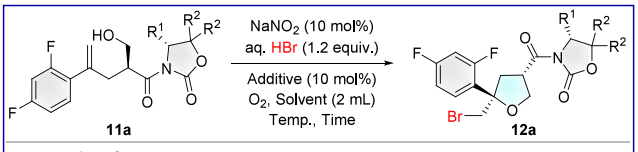
the solvent. To our delight, product **12a** was successfully obtained with a yield of 74% and diastereomeric ratio of 4.4:1 at room temperature (Table 1, Entry 1). Subsequently, the use

Table 1. Optimization of Reaction Conditions[a,b]



Entry	R^1	R^2	Additive	Solvent	Time (h)	Temp. (°C)	Yield (%)	*dr*[c]
1	Bn	H	-	CH_3CN	1	25	74	4.1:1
2	Bn	H	$Cu(OTf)_2/Zn(OTf)_2$	CH_3CN	1	25	80/82	4.1:1
3	Bn	H	$Mg(OTf)_2$	CH_3CN	1	25	87	4.1:1
4	Bn	H	$Mg(OTf)_2$	DCM/EA/THF	1	25	54/70/74	<4.0:1
5	Bn	H	$Mg(OTf)_2$	CH_3CN	12	-20	85	5.1:1
6	Bn	H	$Mg(OTf)_2$	CH_3CN	24	-30	84	7.4:1
7	Bn	H	$Mg(OTf)_2$	CH_3CN	24	-40	Trace	-
8	^{i}Pr	H	$Mg(OTf)_2$	CH_3CN	24	-30	83	6.4:1
9	Ph	Ph	$Mg(OTf)_2$	CH_3CN	24	-30	87	9.3:1
10	Ph	H	$Mg(OTf)_2$	CH_3CN	24	-30	82	8.6:1
11	Ph	Ph	$Mg(OTf)_2$	C_3H_7CN	24	-30	87	7.3:1
12	**Ph**	**H**	**$Mg(OTf)_2$**	**C_3H_7CN**	**24**	**-30**	**89**	**11.5:1**
13	Ph	H	$Mg(OTf)_2$	C_2H_5CN	24	-30	85	8.9:1
14	Ph	H	$Mg(OTf)_2$	C_4H_9CN	24	-30	84	10.3:1
15[d]	Ph	H	$Mg(OTf)_2$	C_3H_7CN	24	-30	75	10.0:1
16[e]	Ph	H	$Mg(OTf)_2$	C_3H_7CN	24	-30	N.R.	-
17[f]	Ph	H	$Mg(OTf)_2$	C_3H_7CN	24	-30	N.R.	-
18[g]	Ph	H	$Mg(OTf)_2$	C_3H_7CN	24	-30	30	10.3:1

[a]Reaction conditions: **1a** (0.2 mmol, 1 equiv), HBr (0.24 mmol, 1.2 equiv), and $NaNO_2$ (10 mol %) were added to solvent at room temperature. [b]Isolated yield. [c]The *dr* value was determined by ^{1}H NMR analysis. [d]KNO_2 was used instead of $NaNO_2$. [e]Without $NaNO_2$. [f]N_2 was used instead of O_2. [g]Air was used instead of O_2. N.R. = No reaction.

of Lewis acids as additives was investigated, and $Mg(OTf)_2$ was the optimized additive leading to approach the desired product in 87% yield, along with the same dr value (Table 1, Entries 2 and 3). Screening different types of solvents did not yield better results (Table 1, Entry 4). The optimized temperature was −30 °C, at which the desired product was obtained with 84% yield and 7.4:1 *dr* (Table 1, Entries 5−7). Different chiral auxiliary groups were subsequently investigated (Table 1, Entries 6, 8−10). The substrate containing a chiral auxiliary group with R^1 and R^2 as phenyl (Ph) was transformed into the product **12a** with 87% yield and 9.3:1 *dr* (Table 1, Entry 9). Meanwhile, the substrate with a chiral auxiliary group where R^1 is a Ph atom and R^2 is a H atom was converted to the desired product with 82% yield and 8.6:1 *dr* (Table 1, Entry 10). Significantly, the nitrile solvent screening demonstrated that butyronitrile emerged as the optimal solvent for achieving the highest diastereoselectivity (11.5:1 *dr*) and giving desired scaffold **12a** in 89% yield when the substrate, possessing a chiral auxiliary group with R^1 as Ph and R^2 as H, was utilized (Table 1, Entries 11−14). The nitrite salt screening process revealed that $NaNO_2$ was the best promoter to yield the better result (Table 1, Entries 12 and 15). The controlled experiments were then carried out and proved that the nitrite salt and O_2 were essential (Table 1, Entries 16−18).

With the optimized conditions in hand, we investigated the scope of this nitrite-catalyzed economic and green bromocyclization. First, the chiral substrates **11** were synthesized from compounds **13** and aldehydes with the assistance of $TiCl_4$, along with excellent diastereoselectivity (*dr* > 99:1). The compounds **13** could be readily prepared from arenes (or aryl bromide) and succinic anhydride as starting materials through a three-step process (for details, please see pages 4 and 6 of SI). The proposed mechanism for the formation of substrates **11** is as follows (for details, please see page 49 of SI): Compound **13** can coordinate with $TiCl_4$ to generate (*Z*)-**Int-II**, while (*E*)-**Int-II** is inhibited due to the steric effect of chiral auxiliary group and substituent of R^2; the species of (*Z*)-**Int-II** would interact with aldehydes to form a favored Zimmerman-Traxler mode of (*Z*)-**Int-II-1**, while the (*E*)-**Int-II-2** is highly disfavored due to severe steric clashes between R^1 and R^2 in the transition state.

Subsequently, a variety of derivatives **11** bearing a chiral auxiliary group (Aux*) were successfully utilized to the stereoselective bromocyclization, leading to access to the corresponding THFs **12** with moderate to excellent yields and satisfactory *dr* values (Table 2). When the aromatic ring was introduced at the 2-position of substituted olefins **11**, desired products **12** were obtained in high yields with moderate to high diastereoselectivities (**12a−12f**). Notably, increasing the loading of $NaNO_2$ would broadly improve the yield of THF scaffolds. Moreover, the secondary alcohols **11** were smoothly transformed to the 2,3,5-trisubstituted THFs in high efficiency (**12g−12s**). In this scenario, the reaction yield remained unaffected by the steric effect, even when a sterically hindered *tert*-butyl group was installed as R^2 substituent on substrate **11** (**12i**). Furthermore, aromatic rings containing both an electron-donating group (EDG) and an electron-withdrawing group (EWG) were well tolerated at the R^2 position of compound **11**, with the desired products **12k−12r** being generated in high-efficiency. Notably, replacement of the aromatic ring with a thiophene moiety exhibited good tolerance, delivering the corresponding compound **12s** in good yield with a high *dr* value. Unfortunately, attempts to employ an *N*-heteroatom as the nucleophilic group failed to form desired product **12t**. The configuration of **12a** was determined by the synthetic processes to posaconazole, and the configuration of **12o** was confirmed by NOE analysis, which could be used to determine the configuration of substrates **11**. In this transformation, two intermediates (**Int-Ia** and **Int-III**) are formed. **Int-Ia** is likely the preferred species due to its lower steric hindrance, leading to the generation of structures such as **12** as major products. In this transformation, the major byproduct is the generated water.

To validate the practical utility of our established methodology, the concise gram-scale syntheses of product **12a** under both batch and continuous flow conditions were smoothly performed (Scheme 2). The desired product **12a** was initially generated in 82% yield with 10.4:1 *dr* under batch conditions, and recrystallization provide the highly pure compound (>20:1 *dr*) in 71% yield. Recent advancements in continuous flow technology have demonstrated remarkable benefits such as increased operational efficiency and safety, exacting control parameters, optimized heat and mass transfer, seamless scalability, easier amplification, and better sustainability.[15] In the beginning, we attempted to carry out the continuous flow reaction with butyronitrile as solvent, and the desired product **12a** was not obtained due to the poor solubility of $NaNO_2$. Replacing butyronitrile with acetonitrile afforded the desired THF scaffold in 86% yield with moderate *dr*, while shortening the reaction time to 7 min (for details, please see page 47 of SI). These results implied that this economic and sustainable

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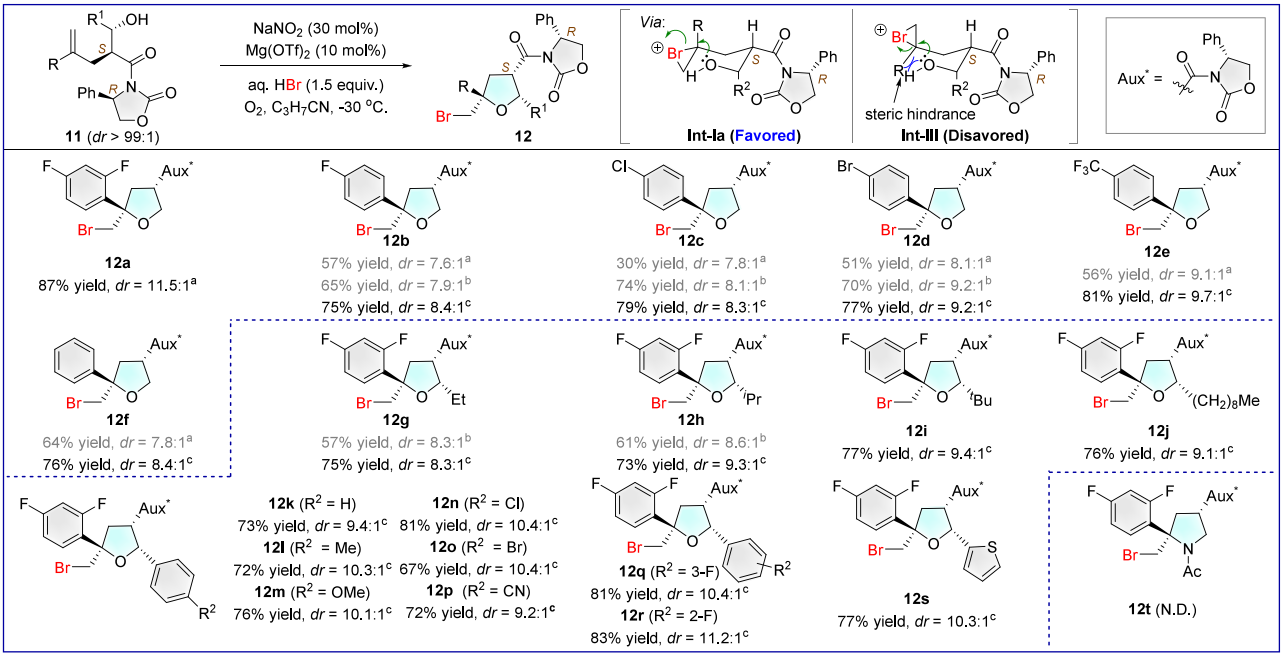
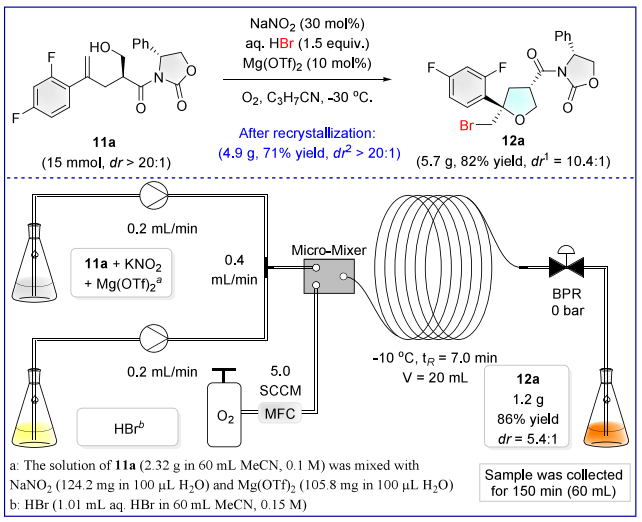
Table 2. Substrate Scope for the Stereoselective Bromocyclization[a,b,c,d,e]



[a]**11** (0.2 mmol, 1.0 equiv), $NaNO_2$ (0.02 mmol, 10 mol %), 48% aq. HBr (0.24 mmol, 1.2 equiv), $Mg(OTf)_2$ (0.02 mmol, 10 mol %) were stirred in C_3H_7CN (2 mL) at −30 °C for 24 h under O_2. [b]**11** (0.2 mmol, 1.0 equiv), $NaNO_2$ (0.04 mmol, 20 mol %), 48% aq. HBr (0.26 mmol, 1.3 equiv), $Mg(OTf)_2$ (0.02 mmol, 10 mol %) were stirred in C_3H_7CN (2 mL) at −30 °C for 72 h under O_2. [c]Standard conditions: **11** (0.2 mmol, 1.0 equiv), $NaNO_2$ (0.06 mmol, 30 mol %), 48% aq. HBr (0.3 mmol, 1.5 equiv), $Mg(OTf)_2$ (0.02 mmol, 10 mol %) were stirred in C_3H_7CN (2 mL) at −30 °C for 72 h under O_2. [d]Isolated yields. [e]The *dr* value was determined by ^1H NMR analysis.

Scheme 2. Gram-Scale Synthesis of Product 12a under Batch and Continuous Flow Conditions



bromocyclization could be a powerful tool for the synthesis of posaconazole.

With the gram-scale operation to access **12a** under batch and continuous flow conditions, we commenced the gram-scale total synthesis of posaconazole (Scheme 3).[4a,5a] Our synthetic procedure to approach key intermediate **1a** began with the auxiliary group removal reaction of **12a** to obtain **10** in 85% yield under reductive conditions, in which the auxiliary group was recovered in 58% yield (for details, please see page 37 of SI). The S_N2 substitution of 1,2,4-triazolylsodium to **10** led to access of the crude product **14**, which could be facilely transformed to the key intermediate **1a** in 55% yield over 2 steps. The synthetic route of the key intermediate **2** was also investigated (for details, please see page 40 of SI), in which methyl(*S*)-2-hydroxypropanoate **15** was subjected to an amidation processes and transformed to the amide **16** in 94% yield. Benzylation reaction of **16** provided the amide **17** in 89% yield. A sequence of Red-Al reduction and hydrazone formation smoothly formed the hydrazone **19** in 78% yield. A formally selective addition of EtMgBr to imine fragment with the assistance of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) gave the key intermediate **20**. A 50 mmol-scale cyclization of **20** and **22** (the latter prepared from **21**) produced 18 g of **23** in 70% yield. A subsequent hydrogenation debenzylation of substrate **23** facilely generated chiral intermediate **2** in 85% yield. Finally, the key S_N2 substitution of intermediate **2** to **1a** was successfully performed on a gram scale under optimized basic conditions, efficiently furnishing the target pharmaceutical posaconazole (for details, please see page 45 of SI). Subsequent recrystallization yielded the final product in high purity (99.57%), as confirmed by HPLC analysis.

In conclusion, we have developed an efficient and concise nitrite-catalyzed bromocyclization of chiral auxiliary-substituted 4-en-1-ol derivatives, enabling the practical synthesis of valuable tetrahydrofuran (THF) scaffolds. This method offers both economic and environmentally friendly advantages aligning with the principles of green chemistry. The gram-scale operation and continuous flow process were successfully performed to access the key THF intermediate with high efficiency. Furthermore, the robustness and synthetic utility of this methodology were convincingly demonstrated through its successful application in the total synthesis of posaconazole. Further studies on the development of more green and

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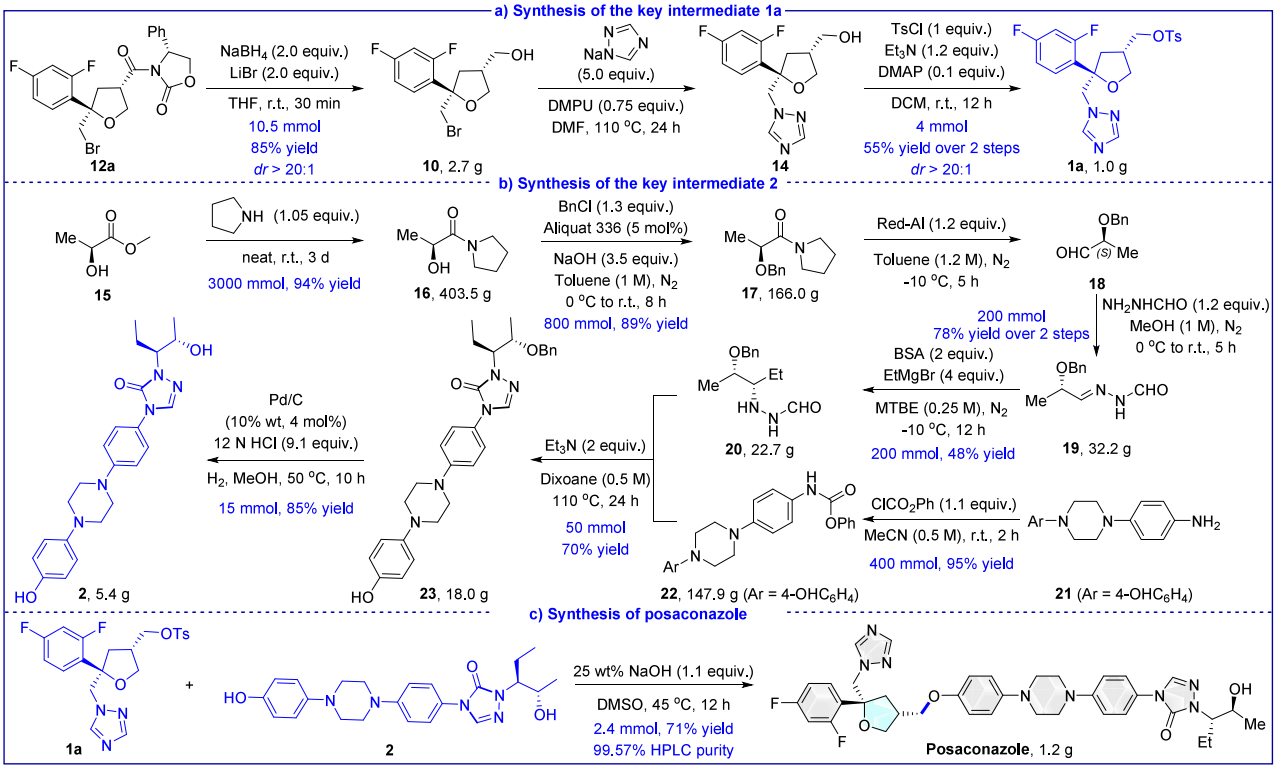
Scheme 3. Gram-Scale Total Synthesis of Posaconazole



economic transformations to access posaconazole are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02469.

Experimental details, additional experimental results, and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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