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Integration of Solventless Reaction in a Multi-Step Process: Application to an Efficient Synthesis of PA-824

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Abstract: In order to improve redundant synthetic processes, the integration of a solventless reaction has proved to be useful for gaining high reaction mass efficiency (RME) as well as reducing the amount of solvents. This concept was applied to synthesis of PA-824, a potential antituberculosis drug. Thus, the solventless ring-opening reaction of glycidyl silyl ether with dinitroimidazole was connected to succeeding solution reactions. The ring-opening of glycidol followed by selective silylation of the primary hydroxy group under solventless conditions was also feasible. As a consequence, the overall yield of the target compound was nearly tripled, and thus the RME values were increased more than 2.5 times while the amount of necessary solvents was decreased to less than 1/3.

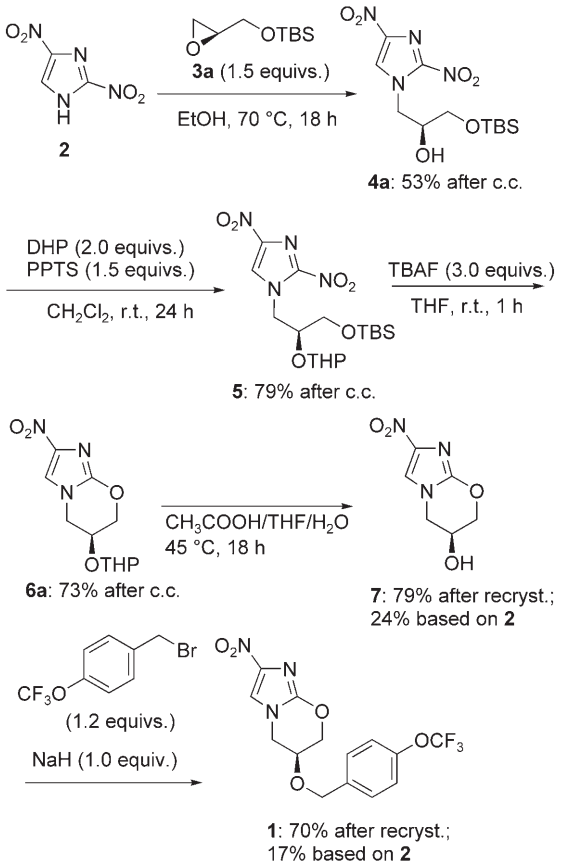
Keywords: atom economy; cesium; glycidyl ethers; imidazoles; one-pot reaction; solventless reaction

Introduction

The improvement of redundant processes for synthesizing pharmaceuticals and fine chemicals is a challenge for chemists in terms of atom economy[1] or process efficiency.[2] For example, the E-factors of pharmaceutical production processes are claimed to be more than 10^3 times larger than those of the most efficient oil-refining processes.[2] Integration of multistep synthetic processes into one-pot provides one of the effective solutions to this problem. Actually, we had previously exemplified that the execution of sequential reactions in one-pot occasionally gave rise not only to the simplification of manipulations but also to an increase in the overall yield.[3] To realize such an integration, the conditions for the respective reactions should be compatible, and, in particular, the common solvents need to be shared through a sequence of the reactions. It may happen, however, that the best solvent system for one reaction is not always the best for the others. The present study stemmed from an idea that the use of a solventless reaction would allow an unrestricted choice of the best solvent in the reaction that follows.

The solventless reactions that have made remarkable advances recently[4] are usually performed by grinding reactants with a pestle in a mortar and, accordingly, few attempts to incorporate such reactions in multistep processes have been undertaken because an apparatus to connect the mechanochemical reactions to the next solution reaction is not readily available. However, we disclosed that mechanical forces are not always required for solventless reactions to occur. Simply standing a solid film obtained by evaporation of the reactant solution drives the reaction faster rather than continuing the reaction in solution.[5] Consequently, we have been intrigued by the integration of a solventless reaction which requires no mechanical forces and a normal solution reaction in one-pot.

PA-824 (**1**) is the target of choice in this study since it has been receiving intensive attention as a potential antituberculosis drug. The effectiveness of this compound was revealed in 1997[6] and phase I clinical trials are now underway by the Global Alliance for TB Drug Development.[7] Scheme 1 depicts the synthetic route for **1** originally put forth by the PathoGenesis group (PG process).[6a] The initial step is the ring-opening of glycidyl TBS ether **3a** by 2,4-dinitroimidazole (**2**), and the resulting TBS alcohol **4a** is converted to the corresponding THP ether **5**. Desilylation of this compound with TBAF spontaneously induces cyclization to give **6a**, deprotection of which provides **7**. The final step is benzylation of this alcohol to arrive at **1** in 17% overall yield. In this paper, we report that the incorporation of a solventless reac-



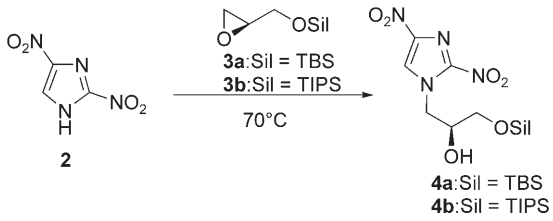
Scheme 1. PG process. DHP = dihydropyran; PPTS = pyridinium *p*-toluenesulfonate; TBAF = Bu_4NF; r.t. = room temperature; c.c. = column chromatography; recryst. = recrystallization.

tion gives rise to dramatic improvements in terms of synthetic and process chemistries.

Results

We ascribed the low overall yield in the PG process primarily to the inefficiency of the initial ring-opening reaction: only a 53% yield of **4a** based on **2** was obtained even by use of 1.5 equivs. of **3a** in EtOH at 70 °C. We thus invoked the solventless protocol. A mixture of **2** and **3a** (1.5 equivs.) was stirred at 70 °C by a magnetic bar in a flask. Note that no mechanical forces were necessary for effective mixing to yield a non-viscous paste, allowing us to execute the ordinary manipulations that are employed in organic synthesis. The yield of **4a** was found to be higher than that of the reaction in EtOH (Table 1). More remarkably, the amount of **3a** could be reduced to 1.2 equivs. The use of the corresponding TIPS ether **3b** provided somewhat higher yields of the TIPS derivative **4b** in comparison with **3a**, hence, prompting us to use this ether in place of **3a** in this study.

Table 1. Ring-opening reaction of glycidyl silyl ethers by dinitroimidazoles.[a]

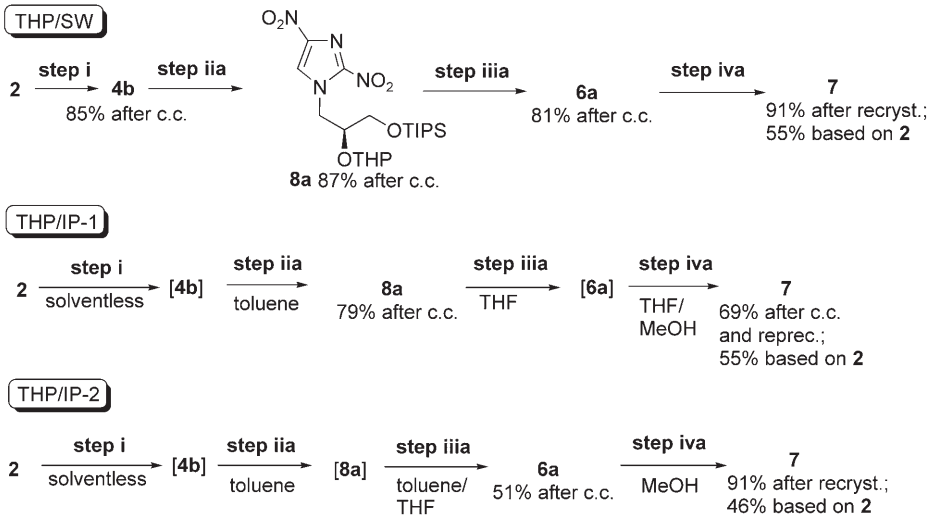


Solvent	Sil [equivs.]	Time [hours]	Yield [%] of **4**
EtOH[b]	**3a** (1.5)	18	**4a** 53
None	**3a** (1.5)	17	**4a** 78
None	**3a** (1.2)	18	**4a** 80
None	**3a** (1.1)	18	**4a** 65
EtOH	**3b** (1.2)	22	**4b** 65
None	**3b** (1.2)	16	**4b** 85
None	**3b** (1.1)	20	**4b** 84

[a] TBS = *t*-$BuMe_2Si$; TIPS = *i*-Pr_3Si.
[b] PG process.

THP Route

With these results in hand, we connected the above-established solventless reaction to the downstream reactions. First, the PG process was modified by use of **3b** in a stepwise manner (THP/SW) (Scheme 2). In addition to the initial solventless step i, the succeeding steps were improved. The yield of the tetrahydropyranylation was increased from 79% to 87% in toluene, which avoided the use of hazardous CH_2Cl_2. The desilylation followed by cyclization (81% yield) step was also superior to that in the PG process (73% yield). Dehydropyranylation was simplified by use of 12 N HCl to give a higher yield (91%) compared to the original method (79%). As a result, the overall yield of **7** was increased to 55% from the 24% yield in the PG process. Then the process was integrated (THP/IP-1). The ring-opening and tetrahydropyranylation reactions (steps i and iia) were run consecutively without isolation of **4b**. To a flask containing the pasty crude product of **4b** resulting from the solventless ring-opening reaction were added toluene, dihydropyran (DHP) and pyridinium *p*-toluenesulfonate (PPTS) in this order. Toluene had proved to be the best solvent for this reaction in separate trials. After 24 h, the desired THP ether **8a** was obtained in 79% yield based on **2**. Then, this compound was converted to **7** without isolation of **6a** by a one-pot two-step operation. After completion of desilylation concomitant with spontaneous cyclization in THF (step iiia), MeOH and one drop of 12 N HCl were added to the reaction mixture to detach the THP group (step iva) to furnish **7** in 69% yield based on **8a**. Preliminarily, MeOH had been found to be the best solvent for the



step i: **3b** (1.2 equivs.), 70 °C, 16 h; **step iia**: DHP (3.0 equivs.), PPTS, (0.2 equivs.), toluene, r.t., 24 h; **step iiia**; TBAF (3.0 equivs.), THF or toluene/THF, r.t., 1 h; **step iva**: 12 N HCl (1 drop), THF or THF/MeOH, r.t., 1 h.

Scheme 2. THP route initiated by solventless reaction (for abbreviations, see Scheme 1).

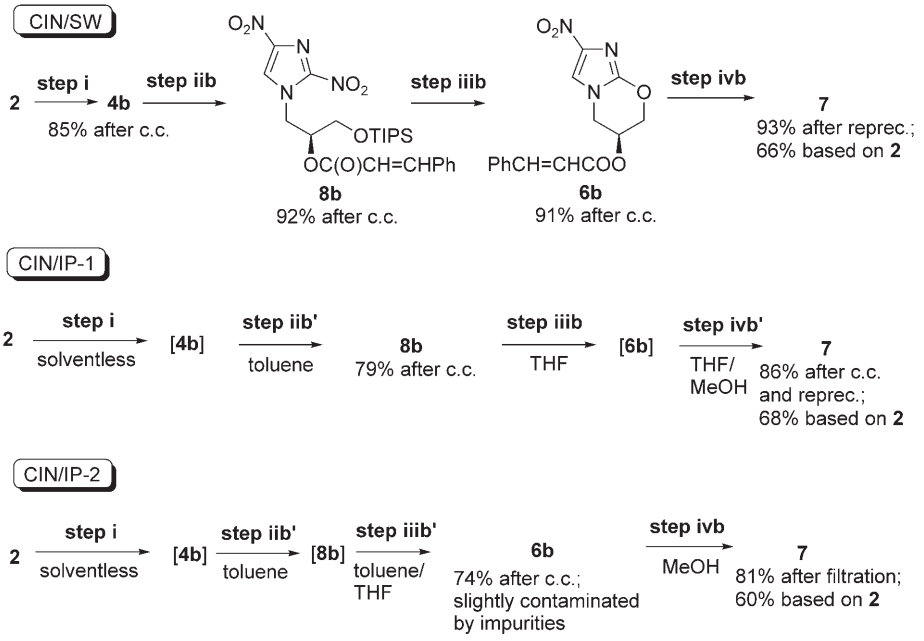
deprotection reaction, yet the reaction proceeded smoothly even in the presence of THF. It should be mentioned, however, that although **7** obtained directly from **6a** could be purified simply by reprecipitation (THP/SW), the crude product obtained by the two-step procedure required column chromatography before recrystallization. The evaluation of the new protocol in comparison with the PG process was made at this stage because the remaining benzylation step is common for both processes. The overall yield of **7** through the four steps in both THP/SW and THP/IP-1 was 55%, showing the advantage of the new protocols over the PG process which provides **7** only in 24% overall yield (Scheme 1). Alternatively, the solventless ring-opening reaction could be connected to the succeeding two steps in one pot as well to directly arrive at **6a**, deprotection of which furnished **7** in 46% overall yield (THP/IP-2).

Cinnamate Route

The use of cinnamyl ester in place of the THP ether as a protecting group gave rise to higher overall yields (Scheme 3). The stepwise cinnamate protocol afforded a 66% overall yield of **7** (CIN/SW). Notably, in contrast to the desilylation of THP derivative **8a** that required 3.0 equivs. of TBAF, **8b** was converted to **6b** with only 1.1 equivs. of TBAF. In CIN/IP-1, the solventless reaction (step i) and cinnamyl ester formation with dicyclohexylcarbodiimide (DCC) (step iib′) in toluene were smoothly integrated to give **8b** in 79% yield based on **2**. Note that the amounts of cinnamic acid, DCC, and *N,N*-dimethylaminopyridine (DMAP) in step iib′ could be adjusted on the assumption that the yield of the step i was the same as that in CIN/SW. Next, the following two steps were integrated. To a THF solution of crude **6b** resulting from desilylation of **8b** followed by spontaneous cyclization (step iiib) were *in situ* added MeOH and Ti(O-*i*-Pr)$_4$ (step ivb′). The deprotective transesterification of **6b** furnished **7** in 86% yield based on **8b**. The reaction took place smoothly even in the presence of THF as well as the adjusted amount of Ti(O-*i*-Pr)$_4$ based on the estimated yield of **6b**, yet the preliminary column chromatography prior to reprecipitation was necessary to obtain pure **7**. The overall yield of **7** based on **2** was 68%. Integration of step i and the succeeding two reactions (steps iib′ and iiib′ where the amounts of reagents were adjusted as above) was also feasible (CIN/IP-2). Although **6b** thus obtained was contaminated by a small amount of inseparable impurities even after column chromatography, deprotection of this product furnished pure **7** in 60% overall yield. Apparently, the cinnamate routes also afforded much higher yields than the original process.

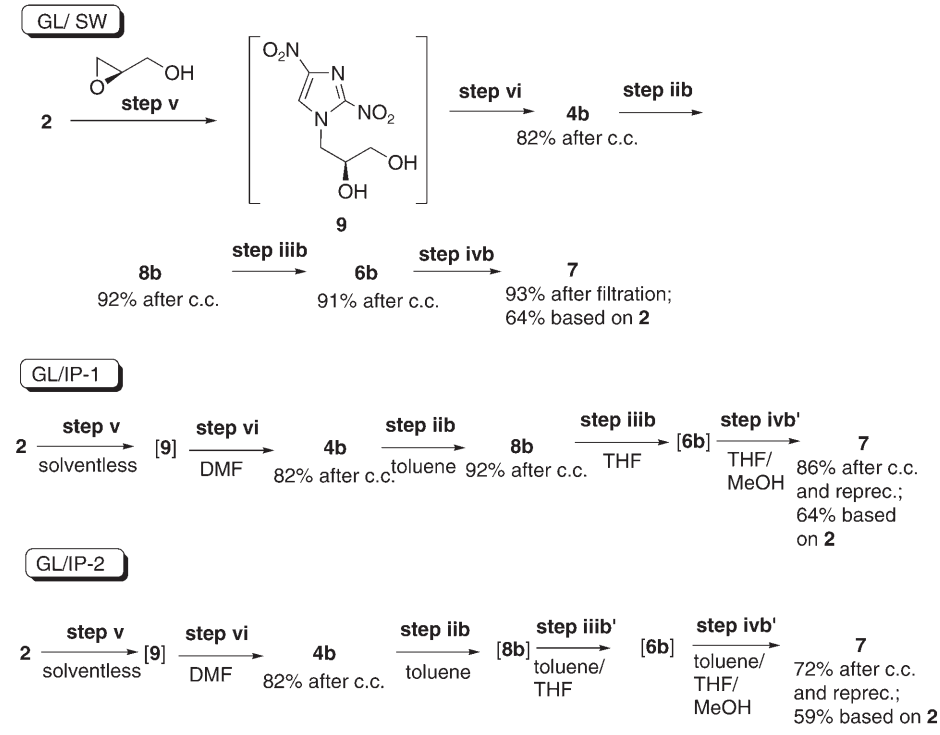
Glycidol Route

The use of the parent glycidol in place of the glycidyl silyl ethers was achieved (Scheme 4). The ring-opening of glycidol by **2** was carried out by catalysis with CsF under solventless conditions. Thus, a mixture of **2**, glycidol (1.3 equivs.) and CsF (0.1 equiv.) was stirred at room temperature for 18 h. To this mixture was added DMF, TIPSCl (2.5 equivs.), imidazole (3.0 equivs.), and DMAP (0.3 equivs.). The solution



step i: **3b** (1.2 equivs..), 70 °C, 16 h; **step iib**: PhCH=CHCOOH (1.2 equivs.), DCC (1.0 equivs.), *N,N*-dimethylaminopyridine (0.2 equivs.), toluene, r.t., 2 h; **step iib'**: PhCH=CHCOOH (1.02 equivs.), DCC (0.85 equivs.), *N,N*-dimethylaminopyridine (0.17 equivs.), toluene, r.t., 2 h; **step iiib**: TBAF (1.1 equivs.), THF, r.t., 1 h; **step iiib'**: TBAF (1.0 equiv.), toluene/THF, r.t., 1 h; **step ivb**: Ti(O-*i*-Pr)$_4$ (0.01 equiv.), MeOH, reflux, 12 h; **step ivb'**: Ti(O-*i*-Pr)$_4$ (0.009 equivs.), THF/MeOH, reflux, 19 h.

Scheme 3. Cinnamate route initiated by solventless reaction (for abbreviations, see Scheme 1).



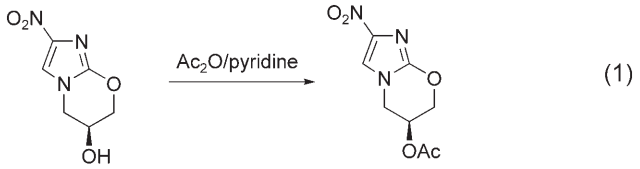
step v: glycidol (1.3 equivs.), CsF (0.1 equiv.), r.t., 18 h; **step vi**: TIPSCl (2.5 equivs.), imidazole (3.0 equivs.), DMAP (0.3 equivs.), DMF, 60 °C, 1 h; **step iib**: PhCH=CHCOOH (1.2 equivs.), DCC (1.0 equiv.), *N,N*-dimethylaminopyridine (0.2 equivs.), toluene, r.t., 2 h; **step iiib**: TBAF (1.1 equivs.), THF, r.t., **1** h; **step iiib'**: TBAF (1.0 equiv.), toluene/THF, r.t., 1 h; **step ivb**: Ti(O-*i*-Pr)$_4$ (0.01 equiv.), MeOH, reflux, 12 h; **step ivb'**: Ti(O-*i*-Pr)$_4$ (0.009 equivs.), THF/MeOH or toluene/THF/MeOH, reflux,19 h.

Scheme 4. Glycidol route initiated by solventless reaction (for abbreviations, see Scheme 1).

was heated at 60 °C for 1 h to furnish **4b** in 82% yield based on **2**. The selective silylation of the primary hydroxy group of intermediate **9** was realized, and the integration of steps v and vi is crucial because **9** is difficult to isolate due to its high solubility in water. Note that a significant drop of the yield of **4b** (15–20%) was observed when the ring-opening reaction was carried out in DMF or CH_3CN solution, indicative of the advantage of the solventless reaction. Then, **4b** thus obtained was transformed to **7** according to the same procedure as CIN/SW to give a 64% overall yield. Next, by integration of the last two steps as in CIN/IP-1, the same overall yield was attained (GL/IP-1). Finally, three steps from **4b** to **7** were integrated (GL/IP-2). Notably, the two-component solvent system for desilylation (step iiib′) and even the three-component solvent system for deprotection of the THP group (step ivb′) worked smoothly although the overall yield was slightly lowered. Finally, **7** obtained according to the above three route was converted to **1** by the PG method in 70% yield.

Enantiomer Excess

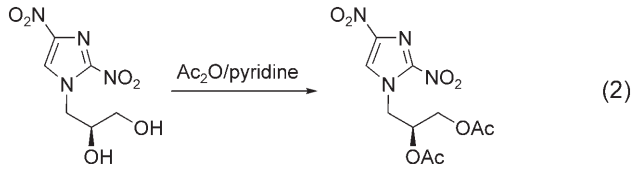
Our protocols have the chiral origin in enantiopure (*R*)-glycidol or its silyl ethers which are prepared from (*R*)-1-choloropropane-2,3-diol of >99% *ee*. Thus, it is of great importance to ascertain that no racemization occurred during manipulations in the above protocols. This was done by measuring the enantiomer excesses of **7** and **1**. Although we could not obtain good resolutions in chiral HPLC of **7** itself, a distinct separation of peaks was attained with its acetate **10** [Eq. (1)], which confirmed >99% *ee* for all



(1)

10: >99% *ee*

compounds produced in this study. The enantiomer excess of **1** also could be determined to be >99%. It is worthy of note that the CsF-catalyzed ring-opening of glycidol proved to induce no racemization. The product diol could be isolated as its diacetate **11** [Eq. (2)]. HPLC analysis of this compound showed the enantiomer excess to be >99%.



(2)

11: >99% *ee*

Discussion

The advantage of incorporation of the solventless reaction is two-fold. First, the yield of the ring-opening reaction is increased. Second, the best solvent can be chosen at will for the next reactions in a one-pot manner. A one-pot reaction in solution was not feasible with the ring-opening reaction of glycidyl ethers. The reaction was best carried out in EtOH, but this solvent was not employable for the next protection steps. The integration of steps i and iia or iib afforded **8a** or **8b** in slightly higher or nearly equal yield as **8a** in THP/IP-1 or **8b** CIN/IP-1 as compared with that in THP/SW (74% = 85% × 87%) or CIN/SW (78% = 85% × 92%). Apparently, these results arose from the choice of the best solvent in the second step. By contrast, further incorporation of step iiia in THP/IP-2 resulted in a decrease of the yield of **6a** (51%) from that in THP/SW (60% = 85% × 87% × 81%) due to the employment of the mixed solvent system which may not be optimal for the reaction.[8] As described above, the ring-opening of glycidol followed by selective silylation could take place in solution, but the yield was lower than that by the solventless protocol.

No significant difference in the overall yields was observed between the stepwise and integrated processes of the three routes. This is ascribed to the counterbalance between the two conflicting factors induced by integration of multi-step processes. The reduced material loss resulting from avoidance of the isolation and purification of the intermediates serves to advantage while subjection of the intermediates contaminated by impurities and by-products to the next reaction works unfavorably. Moreover, the steps iva and ivb′ in THP/IP-1 and CIN/IP-1 or GL/IP-1, respectively, were carried out in THF/MeOH. It is operationally convenient that the THF employed in the former step need not be removed, yet the co-existence of this solvent might have induced a reduction of the yields in the second reactions to some extent. This is reflected in the necessity of the column chromatography prior to reprecipitation for purification of **7**. The similar situation might be true for the steps iiia, iiib′, and ivb′ in THP/IP-2, CIN/IP-2, and GL/IP-2, respectively.

The evaluation of the new protocols initiated by the solventless reactions with reference to the PG process from the viewpoint of process chemistry is summarized in Table 2, in which a comparison is made based on the overall procedure leading to **1**. Simple reaction mass efficiency (RME)[9] excluding reaction and postreaction solvents was determined as a ratio of the mass of product *vs.* the mass of total

Table 2. Comparison between PG and new processes.

	Overall yield of **1** [%][a]	RME[b]	Solvent employed/L[c]
PG process	17	0.053	78800 (141)
THP/SW	38	0.094	59100 (220)
THP/IP-1	38	0.089	49900 (270)
THP/IP-2	32	0.070	30100 (255)
CIN/SW	46	0.136	49500 (247)
CIN/IP-1	48	0.138	46300 (258)
CIN/IP-2	42	0.121	22500 (277)
GL/SW	45	0.091	53200 (272)
GL/IP-1	45	0.093	51700 (284)
GL/IP-2	41	0.086	38700 (324)

[a] TBS = *t*-BuMe$_2$Si; TIPS = *i*-Pr$_3$Si.
[b] PG process.[a] Based on the 70% yield of conversion from **7** to **1**.
[b] RME = 1 produced (kg)/total amount of chemicals employed (kg).
[c] The amount of solvents used in reactions and postreactions to produce 1 kg of **1**; estimated to be accurate within 15%. The amount of solvents used for reactions only are given in parentheses.

chemicals used. These data are based on flask-scale experiments and the conditions given here are far from the optimum in terms of process chemistry.[10] Nevertheless, the essential advantage of the new protocols over the PG process is apparent even at this preliminary stage. The use of the solventless reaction gave rise to higher RME values than the PG process. This is mainly attributable to the increase of yield in the initial solventless ring-opening although the increase of yields in the respective downstream steps also contributes to some extent as is apparent from the comparison between the stepwise processes and the PG process. The RME values of the glycidol protocols are not so high as expected from the relatively high overall yields. This is mainly attributable to employment of excess amounts of TIPSCl and imidazole in step vi. Nevertheless, the absence of a demand for the separate synthesis of glycidyl silyl ethers is highly advantageous from an economical point of view.

There are no significant differences in the RME values between the integrated processes and stepwise processes, a quite natural outcome because the basically same routes are involved in both cases. Thus, the amounts of solvents used for the reactions also do not significantly differ as given in parentheses of the last column in Table 2. On the other hand, big differences emerge if the postreaction solvents employed for work-up, column chromatography and reprecipitation are taken into account. In the stepwise protocols, column chromatographic purification after usual work-up is necessary for three intermediates, **4b**, **8a** or **8b**, and **6a** or **6b**, together with reprecipitation for **7**. On the other hand, the integrated protocols, THP/IP-1 and CIN/IP-1, require column chromatography twice and reprecipitation once. Note that preliminary column chromatography prior to reprecipitation is necessary for purification of crude **7** obtained by the consecutive two-step procedure. Nevertheless, skipping column chromatography for **4b** and **6a** or **6b** in these integrated protocols helps diminish the amount of solvents to a great extent. More favorably, the protocols, THP/IP-2 and CIN/IP-2, are free from the column chromatographic purification of **7** because the crude product can be purified solely by reprecipitation, leading to the least consumption of solvents. In the glycidol protocols, **4b** should be isolated even in the integrated processes, thus consuming larger amounts of solvents. As a whole, the integrated cinnamate routes gave rise to a great improvement from a viewpoint of process chemistry: CIN/IP-1 is the best in terms of RME while CIN/IP-2 in terms of the solvent consumption.

Conclusions

In summary, incorporation of a solventless reaction in integrated processes has proved to be very useful for designing efficient multistep processes. In particular, the flexibility to choose a solvent in the reaction to follow is of great help for integration of the steps. It should be pointed out that the most energy intensive steps in chemical industry are those for separation and purification of intermediates.[11] The integration serves well for saving energy as well as raw materials. The validity of this concept has been exemplified by new efficient protocols for synthesizing PA-824.

Experimental Section

General Remarks

All reactions were carried out under an atmosphere of argon with freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Other solvents such as toluene and DMF were distilled from CaH_2. Silica gel (Daiso gel IR-60) was used for column chromatography. NMR spectra were recorded at 25 °C on JEOL Lambda 300 and JEOL Lambda 500 instruments and calibrated with tetramethylsilane (TMS) as an internal reference. Optical purity was determined by HPLC with a CHIRALCEL OD-H column. Elemental analyses were performed by the Perkin–Elmer PE 2400. (*R*)-Glycidol (99.3% *ee*) was supplied by Daiso Co. Glycidyl silyl ethers **3a**[12] and **3b**[13] were prepared according to the reported procedure.[13]

THP/SW

Product 4b: A powdery mixture of **2** (316 mg, 2.0 mmol) and **3b** (553 mg, 2.4 mmol) was heated at 70 °C for 16 h with stirring by a magnetic bar in a flask. The pasty product was subjected to column chromatography on silica gel (10–30:90–10 EtOAc/hexane) to furnish **4b**; yield: 660 mg (85 %); mp 64–65 °C; $[\alpha]_D^{19}$: +29.5 (*c* 1.00, THF); ^{1}H NMR (DMSO-d_6): δ = 0.97–1.22 (m, 3H), 1.11 (d, J = 5.6 Hz, 18H), 3.64 (dd, J = 10.2, 7.2 Hz, 1H), 3.83 (dd, J = 10.2, 4.7 Hz, 1H), 4.01–4.03 (m, 1H), 4.40 (dd, J = 13.5, 9.2 Hz, 1H), 4.86 (dd, J = 13.5, 3.2 Hz, 1H), 5.39 (d, J = 5.5 Hz, 1H), 8.73 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 11.3, 17.6, 54.0, 65.5, 68.9, 127.1, 141.8; anal. calcd. for $C_{15}H_{28}N_4O_6Si$: C 46.37, H 7.26, N 14.42; found: C 46.32, H 7.48, N 14.27. RME for **4b**: 0.762; required solvents for production of 1 kg of **4b**: 4530 L.

Product 8a: To a toluene solution (10 mL) of **4b** (777 mg, 2.0 mmol) were added DHP (0.547 mL, 6.0 mmol) and PPTS (100 mg, 0.4 mmol). The mixture was stirred for 24 h at room temperature. The reaction mixture was combined with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL × 3). The organic layer was washed with NaCl solution (10 mL) and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (10:90 EtOAc/hexane) to furnish **8a**; yield: 822 mg (87 % as an inseparable 1:1 mixture of atropisomers): ^{1}H NMR (DMSO-d_6): δ = 1.09–1.27 (m, 21H), 1.30–1.84 (m, 6H), 3.18–4.66 (m, 7H), 4.79 4.96 (dd, J = 13.8, 3.4 Hz, 1H), 8.69 (s, 0.5H), 8.81 (s, 0.5H); ^{13}C NMR (DMSO-d_6): δ = 11.2 11.3, 17.6 17.7, 19.1 19.8, 24.6 24.8, 30.1 30.3, 51.6 51.9, 61.9 62.8, 63.3 64.0, 74.1 76.3, 97.9 99.3, 126.9 127.2, 128.3, 141.7 141.8. RME for **8a**: 0.593; required solvents for production of 1 kg of **8a**: 4953 L.

Product 6a: To a THF solution (5 mL) of **8a** (473 mg, 1.0 mmol) was added slowly a THF solution of TBAF (1.0 M, 3.0 mL, 3.0 mmol) at 0 °C. After the solution had been stirred for 1 h at room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added. The organic layer was evaporated and the residue was extracted with $CHCl_3$ (10 mL × 3). The $CHCl_3$ solution was washed with water (10 mL) and brine (10 mL). The residue obtained by drying ($MgSO_4$) followed by evaporation was subjected to column chromatography on silica gel (5:95 MeOH/EtOAc) to furnish **6a**; yield: 218 mg (81 %). RME for **6a**: 0.174; required solvents for production of 1 kg of **6a**: 23208 L.

Product 7: A MeOH solution (6.0 mL) of **6a** (54 mg, 0.2 mmol) and one drop of 12 N HCl was stirred at room temperature for 2 h. The residue obtained by evaporation was recrystallized from MeOH (2 mL) to furnish **7**; yield: 34 mg (91 %; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.625; required solvents for production of 1 kg of **7**: 237 L.

THP/IP-1

Product 8a: A powdery mixture of **2** (316 mg, 2.0 mmol) and **3b** (553 mg, 2.4 mmol) was heated at 70 °C for 16 h with stirring by a magnetic bar in a flask. To the resulting pasty product **4b** were added toluene (10 mL), DHP (0.547 mL, 6.0 mmol), and PPTS (100 mg, 0.4 mmol) at room temperature. The mixture was stirred for 24 h at this temperature. The reaction mixture was combined with saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (10 mL × 3). The organic layer was washed with NaCl solution (10 mL) and dried over $MgSO_4$. After evaporation, the residue was subjected to column chromatography on silica gel (10:90 EtOAc/hexane) to furnish **8a**; yield: 747 mg (79 % based on **2**). RME for **8a**: 0.506; required solvents for production of 1 kg of **8a**: 6780 L.

Product 7: To a THF solution (5 mL) of **8a** (473 mg, 1.0 mmol) was added slowly a THF solution of TBAF (1.0 M, 3.0 mL, 3.0 mmol) at 0 °C. After the solution had been stirred for 1 h at room temperature, MeOH (30 mL) was added. Then, one drop of 12 N HCl was added at 0 °C, and the solution was stirred for 1 h at room temperature. The residue obtained by evaporation of the reaction mixture was subjected to column chromatography on silica gel (10:90 EtOAc/MeOH). Further purification of the product thus obtained by reprecipitation from MeOH (3 mL) furnished pure **7**; yield: 128 mg (69 % based on **8a**; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.102; required solvents for production of 1 kg of **7**: 31634 L.

THP/IP-2

Product 6a: A toluene solution of **8a** obtained as above was combined with THF (10 mL). To this solution was added a THF solution of TBAF (1.0 M, 6.0 mL, 6.0 mmol) at 0 °C, and the solution was stirred at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (10 mL) was added. The organic layer was evaporated and the residue was extracted with $CHCl_3$ (10 mL × 3). The $CHCl_3$ solution was washed with water (10 mL) and brine (10 mL). The residue obtained by drying ($MgSO_4$) followed by evaporation was subjected to column chromatography on silica gel (5:95 MeOH/EtOAc) to furnish **6a**; yield: 275 mg (51 % based on **2**). RME for **6a**: 0.090; required solvents for production of 1 kg of **6a**: 18482 L.

Product 7: An MeOH solution (6.0 mL) of **6a** (54 mg, 0.2 mmol) and one drop of 12 N HCl was stirred at room temperature for 2 h. The residue obtained by evaporation was recrystallized from MeOH (2 mL) to furnish **7**; yield: 34 mg (91 %; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.625; required solvents for production of 1 kg of **7**: 237 L.

CIN/SW

Product 8b: To a toluene solution of **4b** (777 mg, 2.0 mmol) were added cinnamic acid (356 mg, 2.4 mmol) and DMAP (49 mg, 0.4 mmol) at room temperature. Then, a pyridine solution of DCC (1.2 M, 1.68 mL, 2.0 mmol) was added dropwise at 0 °C, and the solution was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with brine (10 mL) and dried ($MgSO_4$). The residue obtained by evaporation was subjected to column chromatography on silica gel (30:70 CH_2Cl_2/hexane) to furnish **8b**; yield: 954 mg (92 %): $[\alpha]_D^{24}$: −86.7 (*c* 1.00 THF); ^{1}H NMR (DMSO-d_6): δ = 0.99–1.13 (m, 3H), 1.04 (d, J = 5.2 Hz, 18H), 3.99 (d, J = 4.6 Hz, 2H), 4.77 (dd, J = 14.3, 8.9 Hz, 1H), 4.96 (dd, J = 14.3, 3.1 Hz, 1H), 5.41 (m, 1H), 6.50 (d, J = 16.2 Hz, 1H), 7.45 (m, 3H), 7.60–7.66 (m, 3H), 8.83 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 11.3, 17.7, 51.1, 62.5, 71.9, 117.0, 127.0, 128.3, 129.0, 130.8, 133.7, 141.7, 142.1, 145.4, 165.3; anal. calcd. for $C_{24}H_{34}N_4O_7Si$: C 55.58, H 6.61,

N 10.80; found: C 55.64, H 6.35, N 10.50. RME for **8b**: 0.598; required solvents for production of 1 kg of **8b**: 3214 L.

Product 6b: To a THF solution (5 mL) of **8b** (519 mg, 1.0 mmol) was slowly added a THF solution of TBAF (1.0 M, 1.1 mL, 1.1 mmol) at 0 °C, and the solution was stirred at room temperataure for 1 h. Aqueous work-up as described in protocol 4 followed by column chromatography on silica gel (20:80 EtOAc/hexane) furnished **6b**; yield: 287 mg (91 %): m.p. 228–230 °C; $[\alpha]_D^{24}$: −115.7 (*c* 1.00 THF); ^{1}H NMR (DMSO-d_6): $\delta = 4.30$ (d, $J = 13.8$ Hz, 1 H), 4.43 (dd, $J = 13.8$, 3.4 Hz, 1 H), 4.64 (m, 2 H), 5.54 (s, 1 H), 6.69 (d, $J = 15.9$ Hz, 1 H), 7.40 (m, 3 H), 7.66–7.74 (m, 3 H), 8.08 (s, 1 H); ^{13}C NMR (DMSO-d_6): $\delta = 46.8$, 62.7, 68.3, 117.2, 118.1, 128.6, 128.9, 130.8, 133.8, 142.1, 146.0, 146.8, 165.4; anal. calcd. for $C_{15}H_{13}N_3O_5$: C 57.14, H 4.16, N 13.33; found: C 57.04, H 3.96, N 13.34. RME for **6b**: 0.357; required solvents for production of 1 kg of **6b**: 17629 L.

Product 7: An MeOH solution (40 mL) of **6b** (315 mg, 1.0 mmol) and Ti(O-*i*-Pr)$_4$ (2.84 mg, 0.01 mmol) was heated under reflux for 12 h. The reaction mixture was filtered through a thin pad of silica gel/MeOH (100 mL) to remove precipitates derived from Ti(O-*i*-Pr)$_4$ and the filtrate was evaporated. After $CHCl_3$ (30 mL) had been added to the residue, **7** was obtained as $CHCl_3$-insoluble powder by filtration and drying under vacuum; yield: 172 mg (93 %; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.541; required solvents for production of 1 kg of **7**: 988 L.

CIN/IP-1

Product 8b: To the pasty product **4b** obtained as above were added toluene (8 mL), cinnamic acid (302 mg, 2.04 mmol) and DMAP (42 mg, 0.34 mmol) at room temperature. Then, a pyridine solution of DCC (1.2 M, 1.43 mL, 1.7 mmol) was added dropwise at 0 °C, and the solution was stirred at room temperature for 2 h. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc (10 mL × 3). The organic layer was washed with brine (10 mL) and dried ($MgSO_4$). The residue obtained by evaporation was subjected to column chromatography on silica gel (10:90–20:80 EtOAc/hexane) to furnish **8b**; yield: 819 mg (79 % based on **2**). RME for **8b**: 0.524; required solvents for production of 1 kg of **8b**: 6172 L.

Product 7: To a THF solution (5.0 mL) of **8b** (519 mg, 1.0 mmol) was slowly added a THF solution of TBAF (1.0 M, 1.1 mL, 1.1 mmol) at 0 °C. The solution was stirred at room temperature for 1 h and combined with MeOH (40 mL). Then, Ti(O-*i*-Pr)$_4$ (2.64 mg, 0.0093 mmol) was added, and the reaction mixture was heated under reflux for 19 h. After evaporation, the residue was subjected to column chromatography on silica gel (10:90 MeOH/EtOAc). Further purification of the product thus obtained by reprecipitation form MeOH (3 mL) furnished **7**; yield: 159 mg (86 % based on **8b**; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.196; required solvents for production of 1 kg of **7**: 31706 L.

CIN/IP-2

Product 6b: A toluene solution of **8b** obtained as above was combined with THF (10 mL) at r.t. Then, a THF solution of TBAF (1.0 M, 2.0 mL, 2.0 mmol) was slowly added at 0 °C, and the solution was stirred at room temperature for 1 h. Aqueous work-up as described in protocol 3 followed by column chromatography on silica gel (30:70 to 20:80 EtOAc/hexane) furnished **6b**; yield: 467 mg (74 % based on **2** with a trace amount of impurities). RME for **6b**: 0.224; required solvents for production of 1 kg of **6b**: 8728 L.

Product 7: An MeOH solution (40 mL) of **6b** as obtained above (supposed to be a pure compound, 315 mg, 1.0 mmol) and Ti(O-*i*-Pr)$_4$ (2.84 mg, 0.01 mmol) was heated under reflux for 12 h. The reaction mixture was filtered through a thin pad of silica gel/MeOH (100 mL) to remove precipitates derived from Ti(O-*i*-Pr)$_4$ and the filtrate was evaporated. After $CHCl_3$ (30 mL) had been added to the residue, **7** was obtained as a $CHCl_3$-insoluble powder by filtration and drying under vacuum; yield: 150 mg (81 %; > 99 % *ee* as diacetate based on HPLC). RME for **7**: 0.472; required solvents for production of 1 kg of **7**: 1134 L.

GL/SW

Product 4b: A flask containing CsF (76 mg, 0.5 mmol) was heated with a flame under vacuum. After cooling the flask, **2** (790 mg, 5.0 mmol) and glycidol (0.431 mL, 6.5 mmol) were charged and stirred by a magnetic bar at room temperature. After 18 h, DMF (5 mL) was added to dissolve the reaction mixture. The solution was combined with a DMF solution (15 mL) of imidazole (1.021 g, 15.0 mmol) and DMAP (183 mg, 1.5 mmol) and stirred for 30 min at room temperature. Then, TIPSCl (2.65 mL, 12.5 mmol) was added at 0 °C and the solution was heated at 60 °C for 1 h. Then, the reaction mixture was combined with saturated $NaHCO_3$ (10 mL) and filtered through a celite pad. The filtrate was extracted with EtOAc (15 mL × 3). The organic layer was washed with water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. The residue was subjected to column chromatography on silica gel (10:90–30:70 EtOAc/hexane) to afford **4b**; yield: 1.592 g (82 %). RME for **4b**: 0.322; required solvents for production of 1 kg of **4b**: 6382 L.

The following procedure is the same as CIN/SW.

GL/IP-1

Conversion of **8b** to **7** without isolation of **6b** was performed in the same manner as CIN/IP-1.

GL/IP-2

Product 7: To a toluene solution (10 mL) of **4b** (777 mg, 2.0 mmol), cinnamic acid (356 mg, 2.4 mmol), and DMAP (49 mg, 0.4 mmol) was slowly added a pyridine solution of DCC (1.2 M, 1.68 mL, 2.0 mmol) at 0 °C. The solution was stirred at room temperature for 2 h and combined with THF (8.0 mL). To this solution was added a THF solution of TBAF (1.0 M, 2.0 mL, 2.0 mmol) at 0 °C and the solution was stirred at room temperature for 1 h. Then, MeOH (80 mL) and Ti(O-*i*-Pr)$_4$ (5.3 mg, 0.019 mmol) were added. The reaction mixture was heated under reflux for 19 h and evaporated. The residue was subjected to column chromatography on silica gel (gradient EtOAc/MeOH). The product thus obtained was further purified by reprecipitation from MeOH to give **7**; yield: 267 mg (72 %; > 99 % *ee* as

acetate based on HPLC). RME for **7**: 0.126; required solvents for production of 1 kg of **4b**: 22889 L.

Conversion of 7 to 1

To DMF solution (5 mL) of **7** (185 mg, 1.0 mmol) and 4-$CF_3C_6H_4CH_2Br$ (0.19 mL, 1.2 mmol) was added NaH (24 mg, 1 mmol) at −50 °C. The mixture was stirred for 1 h at this temperature and 12 h at room temperature. The reaction mixture was combined with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic layer was washed with water (10 mL) and brine (10 mL). After drying ($MgSO_4$) and evaporation, the residue was subjected to column choromatography on silica gel (EtOAc). The product thus obtained was recrystallized from hot methanol (3 mL) to give **1**; yield: 251 mg (70 %); mp 149–150 °C; $[\alpha]_D^{25}$: −44.7 (*c* 1.00 MeOH); > 99 % *ee* based on HPLC; ^{1}H NMR (DMSO-d_6): δ = 4.30 (m, 3H), 4.53 (d, J = 12.2 Hz, 1H), 4.74 (m, 3H), 7.41 (d, J = 7.95 Hz, 2H), 7.50 (d, J = 7.60 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 46.7, 66.6, 67.8, 68.7, 118.0, 120.9, 129.4, 137.3, 142.1, 147.1, 147.7; anal. calcd. for $C_{14}H_{12}N_3O_5F_3$: C 46.81, H 3.37, N 11.70; found: C 46.58, H 3.34, N 11.67. RME for **1**: 0.485; required solvents for production of 1 kg of **1**: 8210 L.

Determination of Enantiomeric Excess for 10

To a pyridine solution (5 mL) of **7** (92.6 mg, 0.5 mmol) was added Ac_2O (0.14 mL, 1.5 mmol) and DMAP (6.1 mg, 0.05 mmol) at room temperature. After the solution had been stirred for 14 h at room temperature, saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous layer was extracted with AcOEt (10 mL × 3). The AcOEt solution was washed with water (10 mL) and brine (10 mL). The residue obtained by drying ($MgSO_4$) followed by evaporation was subjected to column chromatography on silica gel (70:30 EtOAc/hexane) to furnish **10**; yield: 106 mg (93 %): > 99 % *ee* based on HPLC; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.04 (s, 3H), 4.21 (dt, J = 14.0, 2.3 Hz, 1H), 4.37 (dd, J = 14.0, 3.7 Hz, 1H), 4.52 (dt, J = 12.3, 2.3 Hz, 1H), 4.59 (dd, J = 12.3, 1.3 Hz, 1H), 5.39 (m, 1H), 8.06 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.7, 46.7, 62.3, 68.2, 117.9, 142.1, 146.7, 169.6; anal. calcd. for $C_8H_9N_3O_5$: C 42.30, H 3.99, N 18.50; found: C 42.47, H 4.01, N 18.30.

Determination of Enantiomeric Excess for 11

Compound **9** prepared by the procedure GL/SW, pyridine (10 mL) and Ac_2O (1.42 mL, 15 mmol) were added. After the solution had been stirred for 12 h at room temperature, saturated aqueous $NaHCO_3$ (25 mL) was added. The aqueous layer was extracted with AcOEt (30 mL × 3). The AcOEt solution was washed with water (50 mL) and brine (50 mL). The residue obtained by drying ($MgSO_4$) followed by evaporation was subjected to column chromatography on silica gel (50:50 EtOAc/hexane) to furnish **11**; yield: 1.23 g (78 %); > 99 % *ee* based on HPLC; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.95 (s, 3H), 2.05 (s, 3H), 4.21 (dd, J = 12.2, 4.9 Hz, 1H), 4.34 (dd, J = 12.2, 3.8 Hz, 1H), 4.75 (dd, J = 14.4, 8.3 Hz, 1H), 4.83 (dd, J = 14.4, 3.8 Hz, 1H), 5.39–5.44 (m, 1H), 8.80 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.4, 20.5, 50.6, 62.2, 68.9, 126.9, 141.7, 142.2, 169.7, 170.1; Anal. Calcd for $C_{10}H_{12}N_4O_8$: C, 37.98; H 3.82; N, 17.72. Found: C, 37.97; H, 3.68; N, 17.95.

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